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In Memoriam

Joseph Bolivar DeLee

Joseph Bolivar DeLee, long a member of the Advisory Editorial Board of the JOURNAL, born on October 28, 1869, died on April 2, 1942. Paternal preference was for the work of a rabbi but maternal instinct guided the son of Morris and Dora DeLee into and through the professional life of a physician. His graduation in 1891 from the Chicago Medical College, later absorbed by the Northwestern University, was followed by an interneship at the Cook County Hospital. Following this, two years were spent in Europe. His specialization and writings indicate that he was largely influenced in the selection and continuation of his activities by Professor Jaggard, and by Professor Ernst Bumm. The premature death of the former gave great impetus to the career of Dr. DeLee who, at an early age, succeeded his former professor at Northwestern University Medical School.

The constructive work of his life took concrete form in the establishment of the Maxwell Street Dispensary in 1894. Five years later he, with others, established a maternity hospital of 14 beds on Chicago's West Side. These facilities soon became outgrown and a new dispensary was built and later a Maternity Hospital of over 100 beds was completed during World War I. On the occasion of the completion in 1931 of the present Chicago Lying-in Hospital on the campus of the University of Chicago, the older hospital was dedicated to the service and medical education of Negroes under the name of the Provident Hospital. The policy of the University of Chicago Medical School was that of having a Department of Obstetrics and Gynecology with full-time salaried teachers. As volunteer professor he was in charge of the Obstetric Service in the hospital until retired as Emeritus Professor at the usual age.

The Chicago Maternity Center was carefully fostered by him as a continuation of the old Maxwell Street Dispensary. The success of

these institutions has in the past been due to the efforts of this leader and to the staff which worked with him and latterly succeeded him. Joseph B. DeLee was an individualist with high professional and personal ideals and endowed with humanitarian instincts. He threw himself wholeheartedly into the development of his native ability and to the skilled application of his professional attainments toward the accomplishment of his ideals. He was hostile to mediocrity and strove for the attainment of perfection.

He filled a position of magnitude in the field of obstetrics which he helped to elevate in its standards; in the field of education, especially visual, where he pioneered in the development of moving pictures, and in the community life, where he blazed trails in bringing the best of obstetric care into homes lacking minimal essentials of living.

His influence was spread widely by the doctors, nurses, and nonprofessional personnel of the staffs who were under his tutelage. Many students have left his classroom to apply his teachings throughout the States of the Union. He was a star of the first magnitude in the obstetric heavens and only death has dimmed the brilliancy which will continue to illumine the atmosphere of his profession.

An In Memoriam of this leader would be incomplete without mention of the close family ties which assisted him in his early, mature, and later life. This is best illustrated by the formation of the Mothers' Aid group by his sister, Ida DeLee Neuman, who organized the group bearing this name. Since 1904 the Mothers' Aiders have carried on expanding a program of varied activities to support and disseminate the ideas and works of their idol. A feeling of loss pervades his surroundings, but with it there lives a memory of his great service to his profession and mankind which will continue through many decades. This man dies but his influence marches on through decades by his personal contacts, writings, and visual education.

Fred L. Adair.

Original Communications

FURTHER STUDIES ON ERYTHROBLASTOSIS NEONATORUM OF OBSTETRIC SIGNIFICANCE*

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ERYTHROBLASTOSIS neonatorum runs much of its course in utero and produces certain manifestations which are of significance to the obstetrician. It is the purpose of this communication to emphasize certain obstetric features revealed by a study of 55 cases, as well as to inaugurate a second period of study to cover five years. The role played by this disease in infantile mortality was stressed in a preliminary report made in the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY in 1937. Following the completion of a five-year period of study, an obstetric pathologic analysis of 47 cases was published in *Surgery, Gynecology and Obstetrics* (January, 1942).

Several objectives have been held and of these, early diagnosis of the disease, ante partum if possible, or at the time of delivery from a study of cord blood, has received particular attention. The responsibility has been placed upon the obstetrician and the pediatrician in consultation in order to provide prompt treatment. No longer should one wait for the jaundice to deepen, or the pallor to increase, before providing transfusions of compatible blood. It is hoped that early diagnosis and treatment will reduce the high mortality rate and minimize the damage to the liver, brain, and other organs.

Attention has also been directed toward ascertaining the etiology and pathogenesis of the disease. In this regard, important studies of the Rh factor have been carried out by Levine. Finally, a lesion of the placenta, an intraplacental hematoma, containing normoblasts and erythroblasts, most likely of fetal origin, has been observed in a few cases of erythroblastosis. Such a condition could provide for the transmission of the Rh factor of Landsteiner and Weiner contained in the red cells of the infant, or some other agglutinogen as yet unknown, from the fetal circulation to that of the mother. Iso-immunization of the mother is produced, with the formation of anti-Rh agglutinins, as shown

*Read at a meeting of the New York Obstetrical Society, Feb. 10, 1942.

NOTE: The Editors accept no responsibility for the views and statements of authors as published in their "Original Communications."

by Levine, Vogel, Katzin and Burnham. These antibodies are then supposed to pass through the placental barrier to the infant where red cell hemolysis is produced. The rather generalized deposition of hemosiderin pigment in the liver, spleen, kidney, and basal nuclei of the brain is evidence of such destruction. Actual damage is also sustained by these organs. Hematopoietic foci persist beyond the normal range, and are generally regarded as a continuation of the embryonal type of blood formation. In general, the degree of involvement is most marked in the hydropic infants, and is present to a less extent in the icterus, anemia, and hemorrhagic diathesis forms of the disease. The bone marrow is hyperplastic, and contains numerous immature normoblasts and erythroblasts which are also to be found in the hemopoietic foci as well as in the circulating blood.

The obstetrician is in a strategic position to influence the destiny of these infants as well as the mothers and fathers. This is of great importance not only from the standpoint of the erythroblastosis, but also with regard to the mother, should she require a transfusion, as is illustrated by Case 3. Furthermore, he will be called upon to advise the parents with regard to future pregnancies.

CLASSIFICATION

The most prominent clinical feature is selected when erythroblastosis is classified as to type, i.e., hydrops, icterus, or anemia. At times this may prove difficult when two or more occur in the same infant. Recently, the author has shown the need for further differentiation of erythroblastosis and has called attention to the hemorrhagic diathesis type of the disease, and an unclassified group. A complete classification of 55 pavilion and private cases* delivered in the Woman's Clinic is shown in Table I. Proper identification has more than academic value, since prognosis varies with each type of the disease.

The term, "hemorrhagic diathesis," refers to a small group of infants having bleeding from the cord, melena, or bloody vomitus, and skin

TABLE I. CLASSIFICATION OF ERYTHROBLASTOSIS NEONATORUM

	NO. OF CASES	FETAL MORTALITY
Hydrops fetalis	17	100 per cent
Icterus gravis	27	45 per cent
Congenital anemia	4	25 per cent
Hemorrhagic diathesis	4	25 per cent
Unclassified cases (Without hydrops, icterus, anemia, or hemorrhagic diathesis)	3	100 per cent
Total	55	65 per cent
Missed abortion	4	

*Private cases have been included through the kindness of Drs. Craig, Greeley, Harrar, Hawkins, Jellinghaus, McCandlish, Williamson, Wing, Sackett, and Steele.

petechiae, in whom careful studies of the cord blood, placenta, or autopsy data, reveal the presence of erythroblastosis instead of hemorrhagic disease of the newborn. Of four such cases in this group, three mothers had a history of erythroblastosis in a previous child. In none of these was there jaundice, or hydrops, to overshadow the hemorrhagic diathesis. The following report illustrates a typical case.

CASE 1.—Mrs. C. F., aged 31 years, Irish, para 5-0-0-2, has had five previous pregnancies, the first in 1934 was a normal infant. It was followed by 3 infants with icterus gravis, all of whom died. The last one of these was autopsied at another hospital and the typical lesions of erythroblastosis were present. The fifth child was delivered elsewhere in 1940 and was normal in every respect, and no specific therapy had been given during the ante-partum course.

The ante-partum course of the present pregnancy was uncomplicated and the period of gestation was forty-three weeks. Maternal blood studies revealed that the patient was Rh negative (husband positive), the Wassermann was negative, and there was no maternal blood abnormality. Vitamin K was given intramuscularly (4 mg. of thyloquinone, Squibb) several days before delivery, at which time the maternal prothrombin level was 71 per cent of normal, and the icterus index was 4 units (normal 2 units).

The infant developed fetal distress during the twenty-six hours of labor. Delivery was spontaneous, and the infant weighed 4,350 Gm. (excessive size). It was asphyxiated and required CO_2 and O_2 resuscitation.

Cord blood studies were carried out immediately. A prothrombin concentration of 14 per cent of the adult normal was found. The blood was also Rh positive. The icterus index was 20 units. The red blood count was 3,350,000, hemoglobin 16 Gm., and white blood count 74,100; there were 90 normoblasts and 46 erythroblasts per 100 white cells. Many of the latter were immature leucocytes.

The infant developed multiple skin petechiae soon after birth and on one occasion vomited some bloody mucus. It also had some dyspnea. Immediately after birth, 3 mg. of thyloquinone (vitamin K, Squibb) was administered, and an additional 1 mg. was given the following day because the prothrombin level had fallen to 7 per cent of the adult normal. Three transfusions were given in the first days of life. The nucleated red cells had disappeared from the circulating blood by the seventh day. The hemoglobin and red cell count were maintained at normal levels and the infant was discharged on the twenty-eighth day of life in excellent condition.

The placenta weighed 765 Gm., the cord was stained yellow, and the amniotic fluid had a brownish color. Histologic section showed numerous nucleated red cells in the fetal vessels. The villi were large with some edema of the connective tissue (duration of pregnancy was forty-three weeks).

The unclassified group includes three infants who died in utero, and in whom examination of the cord blood and autopsy disclosed unmistakable evidence of erythroblastosis. Had these infants been born alive, they

may have developed clinical icterus or anemia and then would have been properly classified. This type of erythroblastosis, without hydrops, icterus, and anemia, has also been reported in the literature by Salomenson, DeLange, and Ferguson. As a subdivision of this group, four cases of missed abortion have been included as shown in Table I. They occurred in patients having a history of erythroblastosis, two of whom showed unmistakable evidence of erythroblastosis in the placenta. This is an important finding, since the infants were too macerated for histologic diagnosis at autopsy.

INCIDENCE

The incidence of erythroblastosis (all types) is 1:438, as shown in Table II. Wolfe reports an incidence of 1:568. At present, many

TABLE II. INCIDENCE OF ERYTHROBLASTOSIS (ALL TYPES)

(Indoor, Outdoor and Private Services: Jan. 1, 1933, to Dec. 31, 1941)

YEARS	TOTAL NO. OF CASES	NO. OF PREMATURE AND FULL-TERM DELIVERIES	RATIO
1933, 1934, 1935	7	10,819	1:1545
First 5-year study			
1936	8	3,390	
1937	9	3,443	
1938	8	3,632	1:438
1939	7	3,383	
1940 (Twins 1 pr.)	9	3,672	
Total	41	17,520	
Second 5-year study 1941	7	3,504	

more cases are being diagnosed than was the case a few years ago. There is no apparent increase in the incidence judging from the fact that from 7 to 9 cases have occurred consistently in the past six years.

Erythroblastosis is responsible for 3.2 per cent of the fetal deaths and exceeds syphilis, sepsis, and hemorrhagic disease as a cause thereof. The lower rate for syphilis is due, no doubt, to prophylactic ante-partum therapy. It is hoped that such an approach will be discovered for erythroblastosis. Prevention of antibody formation in the mother may be such an objective.

DURATION OF GESTATION

The average duration of pregnancy was 36.4 weeks in the hydropic infants, and those with the other forms of erythroblastosis were usually born nearer term. Generally speaking, the nearer term, the milder was the disease, and the better seemed the prognosis as shown in Table III. Excluding the cases of hydrops, the average duration of pregnancy for infants that survived was 39.9 weeks, whereas, in those that died, it was only 38.6 weeks.

TABLE III. THE RELATION OF DURATION OF PREGNANCY TO BIRTH WEIGHT AND FETAL MORTALITY IN ERYTHROBLASTOSIS

	DURATION OF PREGNANCY WEEKS	BIRTH WEIGHT GM.	MORTALITY RATE %
Hydrops	36.4	3,421	100
Icterus	39.2	3,426	48
Anemia	40.2	3,095	25
Hemorrhagic diathesis	39.1	3,842	25
Unclassified	40.0	3,360	100

The average weight of 3,421 Gm. in the infants with hydrops is excessive for the gestation of thirty-six weeks, and has been attributed to the generalized edema. For the other types of the disease, the weights were within the expected range.

PARITY

Most observers, including Potter and Schumann, have reported erythroblastosis in multiparas. Multiparity is a distinct factor in 85 per cent of the cases as indicated in Table IV. The disease usually ap-

TABLE IV. THE INCIDENCE OF ERYTHROBLASTOSIS IN SUCCESSIVE PREGNANCIES

	TOTAL PREGNANCIES	NUMBER	PERCENTAGE	
First pregnancy	52	8	*15.0*	
Second pregnancy	50	26	52	
Third pregnancy	31	16	51	
Fourth pregnancy	20	8	40	*85*
Fifth pregnancy	12	6	50	
Sixth or over	8	6	76	
Total	173	70		

pears in either the second, third, or fourth pregnancy. Repeated pregnancies serve to increase iso-immunization according to Levine and

TABLE V. PROGNOSIS IN 55 CASES OF ERYTHROBLASTOSIS AS SHOWN BY THE OBSTETRIC HISTORY OF 8 PRIMIPARAS AND 47 MULTIPARAS

	PREGNANCIES BEFORE ERYTHROBLASTOSIS			ERYTHROBLASTOSIS		PREGNANCIES AFTER ERYTHROBLASTOSIS			
	NO. INFANTS	STILLBIRTHS AND NEONATAL	ABORTIONS	NO.	INCIDENCE*	NO. INFANTS	ABORTIONS	ERYTHROBLASTOSIS NO.	ERYTHROBLASTOSIS INCIDENCE*
Primiparas (8 or 15%)	0	0	4**	8	100.0%	0	2	9	100%
Multiparas (47 or 85%)	92	18	12 (7.1%)	47	30.0%	8	8 (32%)†	9	53%

*Omitting abortions.
**Two were induced.
†Four were missed abortions.

his co-workers. However, 8 or 15 per cent of the patients were primiparas, 6 of which had the severest form of the disease, namely hydrops fetalis.

The recurrence of erythroblastosis in subsequent pregnancies has been found to be 100 per cent in primiparas, a 1:1 ratio. In the multiparas, it is 53 per cent, or a 1:3 ratio, as shown in Table V. Such a dominance suggests a definite hereditary influence which will be discussed under the Rh factor. Sickle cell anemia is also believed to be inherited as a dominant mendelian characteristic.

Abortion was not frequent, namely, 7 per cent; although after the appearance of erythroblastosis, it occurred in 32 per cent. There was only one case of habitual abortion, but missed abortion occurred in 4 patients.

RH FACTOR

It has been stated above that women having infants with erythroblastosis appear predisposed to the disease, perhaps on a hereditary basis. However, multiparas may have normal infants after its appearance, as indicated in Table V. Interest centers around a newly discovered blood factor called Rh, which Landsteiner and Weiner found in the red cells of the *Macacus rhesus* monkey. They ultimately showed that the blood of 86 per cent of the random population contained this factor, whereas, the remaining 14 per cent lacked it, and were designated as Rh positive and Rh negative, respectively. The Rh factor is regarded as a dominant mendelian characteristic transmitted by a pair of genes RH and rh. The incidence of genotype RHRH is given as 37 per cent; RHrh is 47 per cent, and rhrh is 15 per cent.

Levine, Burnham, Katzin, and Vogel find that in erythroblastosis 90 per cent of the mothers are Rh negative, and the husbands are Rh positive, just the reverse of the incidence in the random population. The baby is usually Rh positive. They theorize that, under such circumstances, iso-immunization of the mother takes place with the formation of anti-Rh antibodies or agglutinins which pass through the placenta and hemolyze the infant's blood. On this basis they explain the pathogenesis of erythroblastosis. Since erythroblastosis occurs most commonly in the second, third, or fourth pregnancy, the previous pregnancies are thought to have started some iso-immunization of the mother. The stage is now supposedly prepared for the appearance of erythroblastosis in the next offspring.

A consideration of various allelomorphic combinations of the RHRH, RHrh and rhrh genotypes recently described by Landsteiner and Weiner are shown in Figs. 1, 2, and 3.* As can be seen, the father and mother

*These charts have been reviewed by Dr. Karl Landsteiner and approved by him as portraying views published recently in the *Journal of Experimental Medicine*.

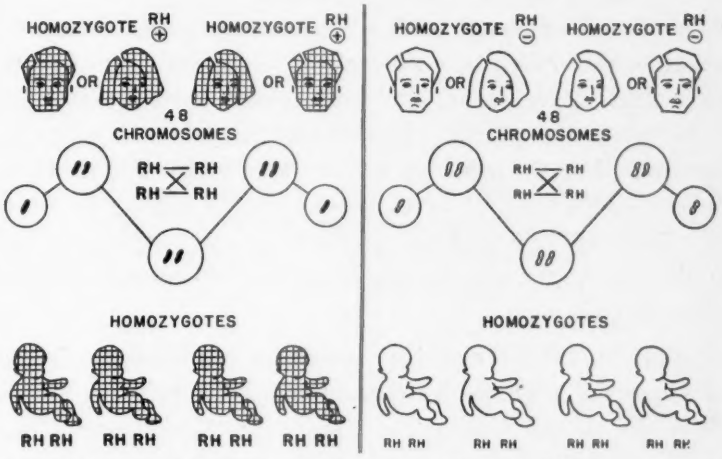

Fig. 1.—Inheritance of the RH agglutinogen. (After Landsteiner and Weiner.)

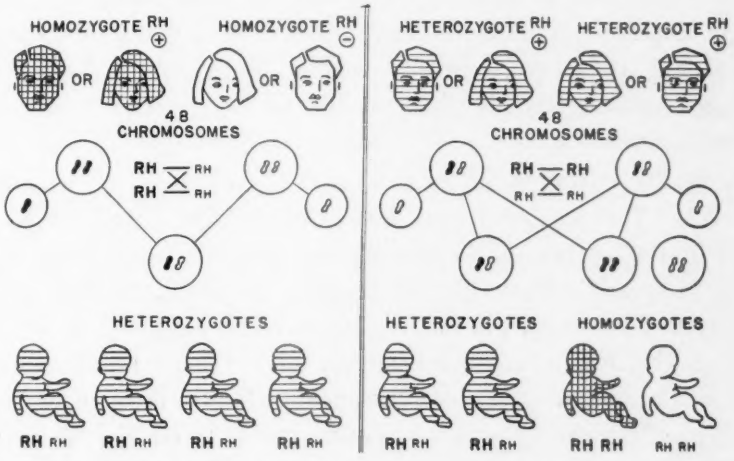

Fig. 2.—Inheritance of the RH agglutinogen. (After Landsteiner and Weiner.)

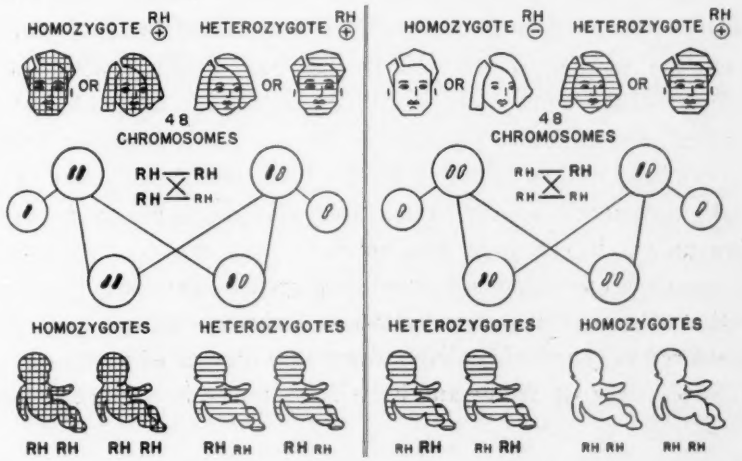

Fig. 3.—Inheritance of the RH agglutinogen. (After Landsteiner and Weiner.)

can be homozygous (RHRH or rhrh) or heterozygous (RHrh or rhRH). The offspring will inherit the Rh factor as a dominant mendelian characteristic from either parent and will become homozygous or heterozygous in terms of the factor. Should both parents be homozygous and Rh negative, all of the offspring will be Rh negative and never be subject to erythroblastosis. The chance of such a mating is, of course, remote. However, in a study of nearly 300 cases, Levine, in a personal communication, states that he has never seen the disease occur under such circumstances.

According to Levine and his co-workers, iso-immunization of the mother is possible when she is Rh negative and the father is Rh positive. Her heterozygous and homozygous infants are, therefore, predisposed to erythroblastosis, since 90 per cent of these mothers are Rh negative. However, as shown in Table V, these mothers have a large number of normal infants prior to the first appearance of erythroblastosis, although after its appearance the recurrence is about 50 per cent. The incidence of 50 per cent corresponds with that obtained by Macklin from a study of cases in the literature.

The results of Rh studies by Levine on 14 of our cases are shown in Table VI. The Rh factor was present in the father and infant, and absent in the mother, in 79 per cent of the cases, which corresponds closely to Levine's figure of 90 per cent. However, there were three exceptions (21 per cent), in that the mothers were Rh positive. Of these, two had Rh positive husbands, and the third was Rh negative. These exceptions present a strong argument against the Rh factor per se as the sole cause of erythroblastosis. Agglutinogens A, B, M, N, or some factor as yet unknown may also iso-immunize the mother with the formation of antibodies which could hemolyze the infant's blood. This concept may explain the frequency of physiologic jaundice of the newborn.

When the mother is Rh positive, iso-immunization with the Rh agglutinogen should not occur, and therefore, the infant should not have erythroblastosis if Levine's theory is correct. This evidence, together with other information including the birth of normal infants before and after the appearance of erythroblastosis, the occurrence in primiparas not immunized by previous pregnancies, involvement of only one of twins, creates a quandary as to the role played by the Rh factor. It appears that other agglutinogens, known or unknown, as well as Rh, must be considered as causes of iso-immunization as illustrated by Case 2. The inheritance of the Rh factor and its relationship to iso-immunization ap-

TABLE VI. THE RH FACTOR IN 14 CASES

Primiparas				
Father	Rh	Positive	2 cases	
Mother	Rh	Negative		
Multiparas				
Father	Rh	Positive	9 cases	
Mother	Rh	Negative		
Baby	Rh	Positive		
Father	Rh	Positive	2 cases	
Mother	Rh	Positive		
Father	Rh	Negative	1 case	Hr factor
Mother	Rh	Positive		
Total			14 cases	

pear to be established, but conclusions as to their role in the etiology of erythroblastosis must be held in abeyance for the present.

The occurrence of erythroblastosis in a mother who was Rh positive and a father that was Rh negative has probably led to the discovery of another atypical agglutinogen which has been called Hr by Levine. This factor may explain the occurrence of erythroblastosis in Rh positive women. Of further interest, is the association of the syndrome called "missed abortion." This case will be described elsewhere by Levine and Javert and is given briefly at this time.

CASE 2.—Mrs. K. F., aged 32 years, German descent, para 2-0-2-1, had a negative Wassermann test. The first pregnancy in 1934 was uncomplicated; the child is living and well. The second pregnancy occurred in 1937, and this infant died on the second day of life of icterus and anemia; erythroblastosis was proved by autopsy. The third pregnancy resulted in a missed abortion with the spontaneous expulsion of the fetus in the thirtieth week of gestation. The fetus weighed 700 Gm., and it was too macerated to provide histologic diagnosis. The fourth pregnancy terminated in another missed abortion in September, 1941, the fetus weighing 1,400 Gm. It was also too macerated for histologic diagnosis. However, histologic sections of the placenta showed unmistakable evidence of erythroblastosis as discussed below under "the placenta."

Blood studies by Levine in the last pregnancy showed the mother to be Rh positive, the father Rh negative. Further studies showed that actually another atypical agglutinogen had been isolated in the blood of the father, which was named Hr. The mother was Hr negative. At this time, the first-born child was examined and was found to be Rh positive, Hr negative.

Complete examinations of the mother's blood has been otherwise negative with regard to plasma prothrombin, vitamin C levels, hemoglobin, counts, and smears. The husband has also been thoroughly examined from every standpoint, including semen analysis by W. H. Cary. He has a normal fecundating specimen.

This case has important obstetric significance because of the two missed abortions which are placed in the unclassified group (see Table I), until more information is obtained with regard to this entity.

The Rh factor has been regarded by Levine and others as a frequent cause of habitual abortion. Table V shows that only 7 per cent of the mothers had abortions before erythroblastosis appeared. It is assumed that all were Rh negative and the husbands were Rh positive. In the primiparas, the noninduced abortion rate was 20 per cent. Neither of these figures are above the incidence ordinarily accepted. However, it occurred to us to study habitual abortion and 12 cases were analyzed. Of these, 9, or 75 per cent, were Rh positive as were their husbands. Unless additional evidence shows the contrary, early habitual abortions should not be attributed to iso-immunization. The Rh factor as a cause of *missed* abortions is suggested in Case 2 and Table V.

CONGENITAL ANOMALIES

Congenital malformations were found in 12, or 22 per cent, of the infants suffering from erythroblastosis; included were: harelip, cleft palate, spina bifida, bilateral hydrocele, supernumerary finger, cervical rib, urethral stricture, and interventricular septal defect. Weber and Scholtz, Vecchi, and Bourret and Lathoud have also reported erythroblastosis associated with congenital anomalies. The incidence of malformations is 40 times greater than Murphy found in the newborn infant. However, he found that when two or more offspring had anomalies, that subsequent offspring had a 50 per cent chance of being deformed. The recurrence of erythroblastosis in multiparas is also about 50 per cent, which suggests very strongly a hereditary basis for the disease.

MATERNAL COMPLICATIONS

The outstanding maternal complications have been the pre-eclamptic type of toxemia and the excessive uterine enlargement, which has been most prevalent in the mothers having babies with hydrops. The relationship of iso-immunization to toxemia was originally reported by Dienst and Ottenberg.

Maternal Mortality.—This was recently reported as none. One mother, however, delivered of an infant with icterus gravis in 1937, has since died following an operation for ectopic pregnancy.

CASE 3.—The patient was given two transfusions of compatible blood, following which jaundice and anuria, with a rise in the blood nonprotein nitrogen to 116 mg., developed. Because of a persisting anemia (red cell count of 1,990,000), a third transfusion was given from a donor whose blood was shown to be compatible with the recipient's serum at 37° C. A chill occurred. Thereafter, the patient was shown to be Rh negative, and all three donors were Rh positive. The patient died on the fifth postoperative day. Similar cases have been reported in the literature by Levine and his co-workers.

THE PLACENTA

The various weights of the placentas in the various groups were as follows:

Hydrops	1,250 Gm.
Icterus	684 Gm.
Anemia	668 Gm.
Hemorrhagic diathesis	784 Gm.
Unclassified	850 Gm.

The infant-placenta ratio (see Table III for weights of infants in the various groups) was about normal, 6:1 in all but the hydrops group where a ratio of 3:1 was seen.

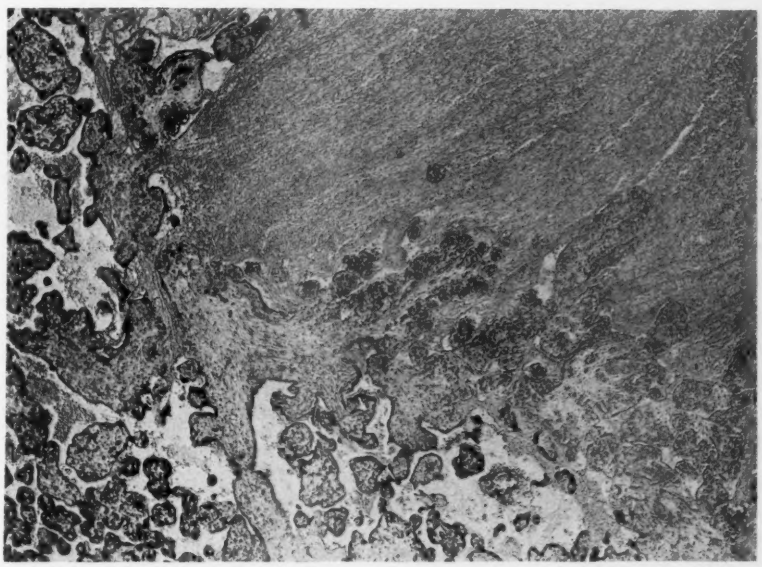

Fig. 4.—Photomicrograph, low power, showing a laminated intraplacental hematoma containing normoblasts and erythroblasts surrounded by a zone of fibroinoid degeneration.

Histologic studies were performed on 34 placentas (15 hydrops, 12 icterus, 3 hemorrhagic diathesis, 2 anemia, 2 unclassified), and 4 missed abortions. Detailed analysis of these studies will be published elsewhere by Traut and Javert. Hellman and Hertig have published a complete description.

The fetal vessels invariably showed an increase in the number of normoblasts and erythroblasts. Syncytial knots were commonly observed. The Langhans layer was seldom present. Intracapillary erythropoiesis was rarely seen. Basophilia was invariably increased and the fetal vessels often exhibited endarteritic changes. At times the amnion was hyperplastic, and pigmented cells were often present in the chorionic plate. Intraplacental hematomas were observed in 8 cases (Fig. 4). Of 10 hematomas, 7 contained nucleated red cells probably of fetal origin.

The hematomas were often laminated. This finding supports the theories of Dienst, Ottenberg and Darrow, that interchange of incompatible maternal and fetal blood in utero can occur and probably produce icterus in the newborn child and eclampsia in the mother as an antigen-antibody reaction. Of the 8 patients, 62 per cent had toxemia. Doi found erythroblasts in the maternal blood of cases of "pregnancy kidney" and eclampsia.

The villi ranged from normal size to huge edematous structures depending on the underlying type of erythroblastosis. This was most marked in the hydrops type. Under such circumstances the fetal vessels were often reduced in size or were absent. The villi in the icterus cases were smaller in size but now and then were edematous.

The placentas of the hemorrhagic, anemic, and unclassified forms of erythroblastosis also showed the above changes, so that a diagnosis could be confirmed. The placentas of 4 cases of "missed abortion" born to mothers after a previous infant with erythroblastosis were scrutinized with interest. In two of these a definite diagnosis of erythroblastosis could be made. This is extremely valuable since the infants were thoroughly macerated so that diagnosis was not possible at autopsy.

The placenta of single ovum twins (Case 2 recently published by Javert in *Surgery, Gynecology and Obstetrics*) showed unmistakable evidence of erythroblastosis in both identical twins, one having the anemic form, the other unclassified. Dr. Samuel Wolfe reports anemia and icterus in twins.

DIFFERENTIAL DIAGNOSIS

In addition to the classification of erythroblastosis as to type as shown in Table I, it is necessary to differentiate physiologic jaundice, prematurity, intracranial hemorrhage, hemorrhagic disease of the newborn, congenital heart disease, congenital syphilis, sepsis neonatorum, obliteration of the bile ducts, familial acholuric jaundice, Winckel's disease, and hypoproteinemia.

MATERNAL BLOOD STUDIES

Routine examination of the maternal blood in 21 cases showed no significant deviation in the red or white counts or in the blood smear. Anemia of pregnancy was very infrequent. The Wassermann was invariably negative. The maternal blood was usually Rh negative as stated above.

The chemical constituents of the maternal blood reflected the toxemia of pregnancy. The elevation in the values for uric acid and the lowering of the CO_2, as Stander has reported, was observed. Of interest, was the elevation of the icterus index in several mothers. This may be attributed to hemolysis of the mothers' blood or liver damage accompanying the

toxemia, with impaired bilirubin metabolism, or to actual absorption of excessive amounts from the fetus.

FETAL BLOOD STUDIES

Immediate advantage in making a diagnosis of erythroblastosis in the newborn infant can be obtained from adequate study of the cord blood. It has been our practice to secure blood by aspiration from the umbilical vein of the cord immediately after expulsion of the placenta as shown in Fig. 5. As much as 100 c.c. can be obtained, provided the cord has not been stripped. It is advisable not to do so in these cases in order to provide blood for study. Using the proper technique, blood can be obtained for typing and cross-matching, chemical studies, blood cultures,

Fig. 5.—Aspirating cord blood directly from the umbilical vein on the fetal surface of the placenta.

vitamin studies and Rh determinations. Such a procedure saves the infant several venipunctures, and avoids delay. Finally, cord blood can be uniformly compared, without considering the day of life the specimen was obtained, as when blood is taken directly from the infant. For example, one of our cases had erythroblastosis, but the first blood smears

TABLE VII. BLOOD STUDIES OF THE UMBILICAL CORD OR ON FIRST DAY OF LIFE*

	R.C.C.	HG (GM.)	C.V.	W.C.C.	N.R.C.	INDEX	
						VOL.	COLOR
5 Hydrops cases	1,51	5.5	25	54,3	43,5	1.5	1.3
6 Icterus cases	3,38	13.1	46	38,4	17,7	1.3	1.4
15 Icterus cases on first day of life	3,09	12.8	--	32.7	14,3	--	1.4
4 Anemia cases	3,5	12.0	--	29.8	13,0	--	1.4
4 Hemorrhagic diathesis	4,1	16.7	47	43.2	24,5	1.3	1.4
3 Unclassified	4,4	15.0	--	43.8	24,4	--	1.25

*R.C.C., red cell count; C.V., cell volume; W.C.C., white cell count; N.R.C., nucleated red cells.

TABLE VIII. SMEARS OF THE UMBILICAL CORD BLOOD ON FIRST DAY OF LIFE

	NORMO-BLASTS	ERYTHRO-BLASTS	IMMATURE POLYS.	RED CELL DIAMETER
9 Hydrops cases	304	98	34	9.5μ
6 Icterus cases	71	14	10	8.0
4 Anemia cases	65	12	5	8.0
4 Hemorrhagic diathesis cases	112	19	9	8.1
3 Unclassified cases	106	19	10	8.1

taken on the tenth day of life failed to show any erythroblasts. Cord blood would have done so.

The results of blood studies in the various types of erythroblastosis are shown in Tables VII and VIII. The blood smears were prepared with ordinary Wright's stain and examined at once. The erythroblasts and normoblasts can be readily identified. Their presence is imperative in making an unquestionable diagnosis of the disease.

PATHOGENESIS OF ERYTHROBLASTOSIS

The importance of the inheritance of the Rh factor and iso-immunization have been alluded to above. The iso-immunization theory of Dienst, Ottenberg, and Darrow, has been invoked by Levine, Katzin, and Burnham to explain the hemolysis of the red cells in erythroblastosis. They assume that hemolysis is the initiating cause of the disease, thereby supporting Parsons, Hawksley, and Gittins. Levine and others state that the baby inherits an Rh positive agglutinogen from the father, which reaches a maternal circulation that is Rh negative. Anti-Rh antibodies, or agglutinins, are formed, thereby iso-immunizing the mother. These agglutinins return to the infant and produce hemolysis of the red cells. Autotransfusions from the infant, with the passage of known or unknown agglutinogens, may be responsible for the iso-immunization of the mother. The hematomas in the placenta indicate the possibility of such transmission. There are others, including Abt, Von Gierke, Salomenson, Clifford, and Hertig, who regard hematopoiesis as the primary cause of the disease; relegating hemolysis to a secondary role. It is futile to argue which of the two are cause or effect; both are present.

Leaving theory behind, it behooves us to study other features of this interesting disease, and among these is the widespread deposition of hemosiderin pigment. Practically all systems are involved. Intracellular pigment can be seen in the basal nuclei of the brain, the so-called "kernicterus" of Schmorl. It occurs in the skin. The chorionic plate often shows it. It is present in the kidneys and especially in the liver.

Liver insufficiency has been shown to exist both pathologically and physiologically. The hydrops cases have a liver parenchyma consisting of hematopoietic foci up to 20 per cent and even more in some infants. If one adds to this the actual cellular degeneration consisting of intra-

cellular pigment, fatty degeneration, cloudy swelling, or actual cellular necrosis, very little actual functioning tissue remains. This may be a factor in the 100 per cent mortality in these infants. When the organs are extremely macerated, the pigment deposits in the liver may be a distinct aid in the diagnosis of erythroblastosis.

The icterus cases showed less liver involvement as evidenced by hematopoiesis and intracellular pigment to a lesser degree. However, bile thrombi, or collections of bile pigment in the biliary capillaries, were more frequent. This can be expected, since the icterus infants survived longer than the hydrops cases, giving the liver an opportunity to metabolize the excessive bilirubin, which it did not do in utero to the same extent, since the ductus venosus shunts the blood around the liver to the vena cava.

Physiologic evidence of liver insufficiency can be obtained from the lowered values in the cord blood for serum proteins, fibrinogen, prothrombin, and bilirubin, shown in Table IX. The hydrops cases showed a greater deviation from the control than did the icterus cases.

TABLE IX. CHEMICAL CONSTITUENTS OF CORD BLOOD IN ERYTHROBLASTOSIS*

	HYDROPS CASES	ICTERUS CASES	CONTROL
Nonprotein nitrogen	(4) 41.7 mg.	(2) 44.0 mg.	35.0 mg.
Uric acid	(1) 7.8 mg.	(2) 3.5 mg.	3.1 mg.
Chlorides	(3) 563.0 mg.	(2) 444.0 mg.	500.0 mg.
Serum proteins	(5) 3.8 Gm.	(8) 5.1 Gm.	5.5 Gm.
Fibrinogen	(2) 0.05- Gm.	(3) 0.1- Gm.	0.3 Gm.
Prothrombin	(2) 5- %	(7) 10 %	23.0 %
Icterus index	(7) 91 units	(8) 48 units	18 units

*Figures in parentheses denote number of cases studied.

Hypoproteinemia (due to the lowered albumin fraction) has been produced in dogs on a low protein diet by Weech and his co-workers. Nutritional edema developed. Deficits in the erythrocytes and hemoglobin were also observed. The hydrops and focal edema and anemia in erythroblastosis, together with the lowered serum proteins, suggests a lack of proteins which provides a metabolic background for this disease. The important role of the liver in maintaining normal protein levels has been demonstrated further by Weech in other conditions and in congenital syphilis.

That erythroblastosis is a generalized systemic manifestation and is not limited to the hemopoietic system is borne out by the following:

1. The rapid return of the blood picture to normal, with the disappearance of nucleated red cells after the child is removed from its intrauterine environment.
2. The dramatic response to prompt transfusion which provides protein as well as red cells.
3. Recovery without sequelae unless permanent damage has been sustained by the organs of the various systems.

The hemopoietic system apparently recovers rapidly in three weeks according to Josephs. The liver is less fortunate, judging from the reports of liver degeneration by deLange and Arntzenius, Klemperer, Hawksley and Lightwood. These sequelae are less prone to occur if treatment is early and adequate as Sobel has intimated and our experience has shown. Juvenile cirrhosis following icterus gravis has been recorded by Boynton and Wyllie, Braid and Ebbs, and Wilson who has also correlated it with degeneration of the lenticular nuclei of the brain. Kernicterus may be a very significant finding. Strong and Marks have emphasized the mental retardation and spastic diplegia in these infants.

ANTE-PARTUM DIAGNOSIS

The mother often exhibits certain signs and symptoms during pregnancy that may serve as a basis for suspecting erythroblastosis in the unborn child. These are as follows, in approximate order of importance: Multiparity, Rh negative mother, Rh positive father, excessive uterine enlargement, yellow brown amniotic fluid, premature labor, Irish nationality (32 per cent) increased icterus index, erythroblastosis in a previous infant, toxemia, fetal distress before and during labor, intrauterine death of the fetus, missed abortion, systolic bruit of fetal heart in utero, x-ray of fetus showing halo and Buddha-like habitus.

There is usually no history of sterility which speaks for the normalcy of the ova and sperm. The high incidence in the Irish women is probably due to the fact that they do not use contraception and are prone to have repeated pregnancies and therefore more infants with the disease. The birth of normal infants in about 50 per cent of the multiparas following the appearance of erythroblastosis, and the birth of many normal infants before the disease appeared, suggests that both parents are heterozygous Rh+, or homozygous Rh– and heterozygous Rh+, as indicated in Figs. 2 and 3, so that one or two Rh negative infants are produced which escape the disease. In primiparas, with recurrence of the disease apparently 100 per cent, the parents are probably homozygous Rh positive, homozygous Rh positive and negative, or homozygous Rh positive and heterozygous Rh positive, as shown in Figs. 1, 2, and 3.

TREATMENT OF THE MOTHER AND INFANT

With regard to the mother, every effort should be made to make an intrauterine diagnosis of the disease, using criteria stated above. The titer of anti-Rh agglutinins can be followed in the mother. Toxemia should be anticipated. A diet adequate in protein, minerals, and vitamins is important. Interruption of the pregnancy and cesarean section should only be performed for maternal indication.

In suspected cases, analgesia and anesthesia are interdicted, because intrauterine asphyxia and asphyxia neonatorum are present in a large

percentage of these infants. Fetal distress is, therefore, frequent (56 per cent) and was largely responsible for a high operative delivery rate. Local infiltration is preferred for the episiotomy.

Therapeutic abortion was not performed on the indication of erythroblastosis alone. However, with the recurrence of erythroblastosis as 50 per cent in multiparas and nearer 100 per cent in primiparas, it seems that some consideration should be made. On the same basis artificial insemination with donor and recipient of the same blood group and Rh negative seems to merit investigation.

With regard to the treatment of the infant, all authorities agree on the necessity of prompt and frequent transfusions. As many as a dozen averaging 60 c.c. in amount may be necessary in the first days of life. The whole blood apparently supplies protein, prothrombin and red cells. The dramatic response to this form of therapy indicates correction of an underlying metabolic disorder. With transfusions, the mortality rate has been lowered from 85 per cent to 73 per cent as shown in Table X. In 1941, the mortality rate was lowered still further to 14 per cent; the only deviation in the treatment was the administration of vitamin K directly to the child at birth; from 2-4 mg. were injected intramuscularly. No hydropic infants, however, were born that year.

TABLE X. FETAL MORTALITY IN ERYTHROBLASTOSIS

YEARS	TOTAL NO. OF CASES	MORTALITY	
		NUMBER	PER CENT
1933, 1934, 1935	7	6	85
First 5-year study, 1936-1940	41	29	73
Second 5-year study, 1941	7	1	14
Grand Total	55	36	65

Early diagnosis and prompt treatment are of great importance. Antepartum notes calling attention to the possibility of the disease will make the obstetrician wary at the time of delivery. The golden-colored amniotic fluid, yellow vernix, fetal distress, etc., should arouse suspicion. Cord blood studies should be performed on every case whether obvious or suspicious. Hours and days of delay are to be avoided and immediate transfusion should be given. The mortality rate will be reduced, and the sequelae should be less serious. Advanced and neglected cases die fortunately, although a few survive and develop juvenile cirrhosis, mental deficiency, and spastic diplegia. When the disease is less severe, however, and the treatment is early and adequate, these infants are often normal and healthy.

SUMMARY

A classification of erythroblastosis based on 55 cases is presented.

The incidence of the disease is 1:438.

The mortality rate appears to decrease in infants born nearer term.

Primiparas having infants with erythroblastosis seem prone to have subsequent babies with the disease, whereas, the recurrence in multiparas is about 50 per cent. Such a relationship points to a dominant mendelian characteristic inherited from the parents, and the Rh factor was discussed from this point of view.

An intraplacental hematoma was found in 8 cases. These were of varying age, and contained numerous normoblasts and erythroblasts most likely of fetal origin. Such a lesion provides for the transmission of the Rh agglutinogen, or some other factor as yet unknown, from the fetal circulation to that of the mother. In such a manner, iso-immunization of the mother could take place.

The formation of antibodies in the mother, with the passage of these through the placenta into the fetal circulation is probably responsible for the red cell hemolysis and the widespread deposition of hemosiderin pigment which characterizes the disease.

The chief maternal complications were toxemia of pregnancy and excessive uterine enlargement. Congenital anomalies in the infants were frequently observed. The relationship of erythroblastosis to missed abortion was seen in several patients.

Early recognition of the disease, in the delivery room aided by studies of the cord blood, affords an excellent opportunity for prompt treatment. Histologic studies of the placenta are confirmatory.

Damage to the internal organs, particularly the liver, is borne out by pathologic and physiochemical studies.

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DISCUSSION

DR. ALEXANDER A. WEECH.—Dr. Javert's observations have dealt with many features which I, as a pediatrician, have had no chance to observe and am therefore not able to discuss. It is better that the occasion should be taken to introduce items which come within the pediatrician's sphere of observation.

Discovery of the association between the Rh antigen and erythroblastosis is among the most brilliant findings of medical literature in recent years. The association is so impressive as to carry conviction of etiologic relationship. Like Dr. Javert, however, I feel that we do not yet understand fully all of the features which

belong to the disease. The Rh antigen exists on the surface of the red blood cells; so far as I know, it has not been demonstrated in any other tissue cells. The reaction between antibody and antigen is manifestly one of intravascular hemolysis and the result is severe anemia. We are entitled to ask whether or not such a reaction can explain the widespread lesions of the disease. The brain may be severely damaged. Infants who die may exhibit stained basal ganglia (kernikterus); infants who survive may later show various types of cerebral palsies. We do not yet have a satisfying explanation of the mechanism of this cerebral injury. Anemia, which does not respond to iron or liver therapy and which is relieved only temporarily by transfusion, often persists for many months. It seems impossible that Rh antibody can persist in the infant circulation for so long a time. One is led to inquire what can be the cause of such long-lasting and apparently hypoplastic anemia. Dr. Javert has reported histologic evidence of severe liver damage in these infants. I can confirm his finding on the basis of analyses of serum from infants who have not died. The serum bilirubin in these cases almost always reacts directly to the Van den Bergh test. The type of bilirubinemia is therefore different from that encountered in physiologic jaundice. The presence of directly reacting bilirubin in the serum is generally interpreted as evidence that bile is regurgitating from the bile ducts into the blood stream, that is, it implies damage or destruction of liver cells. The factors responsible for this hepatic injury are not yet understood.

I must not close these remarks without mentioning the chief concern which haunts the pediatrician when he is asked to treat one of these infants. There is no doubt that prompt and repeated transfusion will often result in the saving of life. Is the treatment justified if the infant is destined to become a cerebrally defective child? Dr. Katharine Merritt, my colleague at the Babies Hospital, has recently assembled our experience on this point. Among 12 infants who survived the initial period of icterus gravis, 9 are healthy and 3 are defective. We have sought, so far without success, to discover what signs or findings in the afflicted infant might presage the final outcome. We can only state at this time that neither the total serum bilirubin nor the amount of directly reacting bilirubin is a reliable index upon which to base prognosis.

DR. LYMAN BURNHAM.—I would like to emphasize the danger of transfusion in the mothers of these babies. This was one of the original clinical observations which gave rise to the theory of iso-immunization as the cause of erythroblastosis. This danger consists of destruction of the transfused blood, resulting in anuria, uremia, and frequently death. It is caused by the same antibodies in the mother which bring about destruction of the baby's blood in utero, namely, the anti-Rh agglutinins, in 90 per cent of the cases.

Such transfusion accidents have occurred three times in one hospital in the past two years and have accounted for three deaths in the Metropolitan area in the past month of January.

Therefore, when erythroblastosis is present, has been present, or may be present, the mother's life will be jeopardized by transfusion unless special precautions are taken. These consist of using Rh negative blood for the Rh negative mothers, together with the compatibility test as modified by Dr. Levine.

We now know that, in addition to erythroblastosis, iso-immunization accounts for some of the hitherto unexplained cases of anemia of the newborn, fetal death in utero, unexplained stillbirths or neonatal deaths, and possibly some of the cases of habitual abortion. Hence, transfusion should also be avoided in these suspicious cases, if possible. The use of plasma will tide over many a patient where blood was formerly thought to be required.

DR. HAROLD MIXSELL.—We have had several cases of this disease at the Woman's Hospital. I am happy to say that we diagnosed them fairly early. We

believe in immediate transfusion. From the clinical standpoint, we make our diagnosis from the family history, for the condition certainly occurs in families in the second, third, or fourth pregnancy and usually in prematures.

DR. ANDREW A. MARCHETTI.—More emphasis should be placed on the size and weight of the placenta. In the hydrops type of erythroblastosis, it is particularly important. Here the ratio of the weight of the placenta to the baby is usually 1:3, whereas in the icteric type and that with congenital anemia, as in normal pregnancy, the ratio is about 1:6. Where a large placenta is found in relationship to the baby, the placenta should be studied with much more care.

In the normal placenta we find very few nucleated red cells and normoblasts. When the number of these cells is considerably increased, or when one finds even one erythroblast, suspicion should be aroused. Seldom, if ever, do we find normoblasts and erythroblasts in the laminated types of placental hematomas associated with normal pregnancy. There were 8 cases in which we found numerous erythroblasts and normoblasts in hematomas and in every instance the baby had erythroblastosis.

DR. WILLIAM H. CARY.—I joined Dr. Javert in investigating the fertility of some of the husbands in the cases he reported tonight. These patients were all highly fertile and the male specimen showed in its morphology nothing significant, in my opinion, which would aid in determining the etiology of the disease.

DR. JAVERT (closing).—We are not quite as pessimistic about the future of these infants as Dr. Weech is. I think he is basing his statements in part on past performance, which means beginning treatment on the third, fourth, or fifth day of life. We are stressing early treatment one or two hours after birth. Under such a regimen I think these infants will show fewer sequelae. The sequelae Dr. Weech has mentioned, namely, cirrhosis of the liver and lenticular degeneration in the brain, are, however, extremely important, and the occurrence of mental retardation has been pointed out by a number of investigators.

Normoblasts in the blood smear on the second or third day of life may occasionally be found, particularly in premature infants. It is seldom, however, that normoblasts are seen at this time in normal, full-term infants. The rate of maturation of nucleated red cells in the blood stream is so rapid that unless a diagnosis of erythroblastosis is made from cord blood, it is sometimes difficult to do so in three or four days. It is thought also that the rate of disappearance of the nucleated red cells may serve as a basis for prognosis, as well as the bilirubin levels which Dr. Weech mentioned. For example, if a child is born with 200 nucleated red cells in the cord blood, they may be reduced to 100 by the third day, to 25 by the fourth day, and at the end of the first week there may be none at all. Consequently, the gradual disappearance of the nucleated red cells may provide a basis for prognosis.

Dr. Burnham brought up the question of transfusion in pregnancy, as well as in cases of erythroblastosis. There were two mothers in the group who received transfusion. One developed a typical eclamptic seizure during the administration of the blood, the nonprotein nitrogen rose to 70 and the uric acid to 12, and the patient was considered as having eclampsia of a post-partum type. She survived. There has been another patient.

The importance of the Rh factor in sterility is an extremely important question. On the other hand, the fertility of this group of patients is extremely high, as Dr. Cary has stated. These mothers have had repeated pregnancies, so I wonder if the Rh factor per se has any actual significance as far as sterility is concerned.

END RESULTS IN THE TREATMENT OF CARCINOMA OF THE CERVIX*

A Fifteen-Year Report, 1921-1936

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ON TWO previous occasions, in 1931 and in 1936, the senior authors published five- and ten-year end-results obtained in the treatment of carcinoma of the cervix on the Gynecological Ward Service at Jefferson Medical College Hospital.[1, 2]

The first report embraced a study of 63 patients seen between Sept. 1, 1921, and Sept. 1, 1925, of whom 57 received treatment, 4 with combined surgery and irradiation and 53 with irradiation only. The absolute salvage, patients alive and apparently free of carcinoma when the report was made, was 14.2 per cent and the relative salvage was 15.7 per cent. The relative five-year salvage in this group was 20.7 per cent. The term "five-year salvage" includes those additional patients who had survived treatment for five years or more but had eventually died, either of carcinoma or of intercurrent disease. The follow-up of this group was 96.8 per cent.

The second report added 93 additional patients observed from Sept. 1, 1925, to Sept. 1, 1930, creating a total of 156, of whom 146 were treated, between 1921 and 1930. This survey showed an absolute salvage of 19.2 per cent, a relative salvage of 20.5 per cent, and a relative five-year salvage, as previously explained, of 25.3 per cent. The follow-up figure at this time was 96.1 per cent.

The present study adds 137 patients seen, of whom 131 were treated between Sept. 1, 1930, and Sept. 1, 1936, a grand total for the fifteen-year period of 293 patients seen and 277 treated, with a follow-up figure of 97.2 per cent (Table I). Approximately 7 per cent of the

Table I. Patients Observed, Follow-Up, 1921-1936

	TOTAL	FOLLOW-UP	PER CENT
Patients seen	293	285	97.2
Patients treated	277	271	97.8

lesions were classified histologically as adenocarcinoma, the remainder being squamous cell type.

*Read at a meeting of the Obstetrical Society of Philadelphia, Jan. 8, 1942.

Sixteen patients were untreated for various reasons. Ten were in Group 4 and were considered too far advanced for treatment with one exception; this patient signed a release and was treated elsewhere. Five patients in Group 3 signed releases, of whom 2 were subsequently treated elsewhere. One patient in Group 5 signed a release.

Of the 8 untraced patients, 2 were in Group 4 and untreated as just mentioned; 4 were in Group 3 and were lost sight of soon after treatment; all are undoubtedly dead. Three, one in Group 2 and 2 in Group 3, had survived treatment seven, eight, and twelve years, respectively, when last seen or heard from. These latter 3 are considered as dead for statistical purposes but efforts are constantly being made to establish proof of their demise.

A larger group of patients carefully observed over a longer period of time permits of the comparative study of various interesting features relative to grouping, age incidence, types of treatment with variations in technique, and numerous other problems concerned with the management of cervical carcinoma. Much that has been said in general in our previous reports need not be repeated in detail but merely commented upon except where further discussion is enlightening.

EXTENT OF INVOLVEMENT

From the beginning we have consistently used the classification of the late Henry Schmitz in estimating the extent of involvement. It is simple, direct and in our opinion more comprehensible than the classifications suggested either by the American College of Surgeons or by the Health Organization of the League of Nations. The personal equation can never be entirely eliminated in any system of physical examination, but the probability of error is perhaps decreased if a less complicated plan is followed. Our entire series of patients, therefore, have been grouped consistently, and no attempt has been made to re-classify them in accordance with the League of Nations "Atlas," for we doubt the accuracy of such a revision in retrospect. Each patient when primarily seen has been grouped in accordance with our best judgment, and this grouping has been maintained for the duration of that particular patient's life. In other words, if a Group 3 patient has shown unusual regression following treatment, we have not seen fit to reclassify her as a possible Group 2, because confusion might result all along the line if this procedure were followed repeatedly. If renewed activity of the lesion is seen after primary irradiation, and further treatment is instituted, that patient's initial classification remains the same. In Group 5 we have placed all patients whose primary treatment has been elsewhere. This includes not only irradiated patients but also those who exhibited carcinoma of the vaginal vault following panhysterectomy or who showed evidence of recurrence elsewhere. This plan has simplified our classification considerably.

As shown in Table II, early cases (35) constitute barely 12 per cent of the patients observed. This figure varies little from that noted in our previous reports. The vast majority of the patients (238) exhibited advanced lesions (Groups 3 and 4), constituting 81 per cent of the series, while 20 of the patients (6.8 per cent) had received primary treatment elsewhere (Group V). These figures are discouraging, for

TABLE II. EXTENT OF INVOLVEMENT (SCHMITZ CLASSIFICATION)

GROUP	NO.	PER CENT
1	5	1.7
2	30	10.2
3	213	72.6
4	25	8.5
5	20	6.8

they would seem to show, in our experience at least, that patients seen with a relatively early lesion are comparatively rare. It cannot be denied, however, that errors in judgment may put patients in Group 3, when they might conceivably have been placed in Group 2. Parametrial induration and even fixation may sometimes represent an inflammatory reaction that recedes with treatment; it is this possibility that can well give rise to the controversy about reclassification.

AGE INCIDENCE, PARITY, RACE

Reference to Table III calls attention to one fact that cannot be overemphasized, the astonishing proportion of patients who exhibit cervical carcinoma before they attain the age of forty. The prevalence of the disease is so often associated in the mind of the physician with the later decades of life that the possibility of an earlier appearance is discounted. Thus valuable time is lost in diagnosis and institution of treatment. As a matter of comparison, the present figure of 27 per cent is somewhat lower than that noted in our previous report which was 29.4 per cent. The youngest patient seen was a twenty-two-month-old infant; the youngest adult was twenty-two and the oldest patient eighty-four.

TABLE III. AGE INCIDENCE, PARITY, RACE

DECADE	NUMBER	PER CENT
1- 9	1	0.3
10-19	0	0.0
20-29	10	3.4
30-39	68	23.2
40-49	87	29.7
50-59	80	27.3
60-69	42	14.3
70-79	4	1.3
80-89	1	0.3
Youngest, 22 mo.; oldest, 84 27 per cent under age of 40		
Nulliparas	25	8.5
Negroes	29	9.8
Jewish	3	1.0

It would be superfluous to present statistics relating to the appearance and duration of symptoms prior to treatment. Irregular vaginal bleeding, both pre- and postmenopausal, generally accompanied with discharge, has usually been present for periods of time, ranging anywhere from a few months to a year and a half before carcinoma was eventually discovered and treated. Neither should it be necessary to repeat the familiar story of delay in investigation for which both the patient and the doctor alike must share responsibility; delay in diagnosis because of undue modesty, apprehension, lack of consultation, failure of adequate examination, and faulty selection of treatment. Too often abnormal bleeding is assumed to be of a functional nature and hormonal therapy is instituted without thorough pelvic investigation and elimination of organic disease. It must be conceded, however, that in exceptional instances cervical carcinoma may develop rapidly, and even extensively without the occurrence of subjective or objective symptoms and signs. Hence the desirability of routine pelvic examinations with frequent biopsies is unchallenged. Catharine Macfarlane[3] and her group have shown what can be accomplished in this respect. The importance of prophylactic biopsy with cauterization or trachelectomy as indicated should be constantly stressed. In our own experience this has revealed unsuspected carcinoma in several instances.

The percentage of nulliparous patients observed is 8.5; in the previous presentation, the figure was 5.7; both these figures have a significance that should be appreciated. The percentage of negro patients has decreased from 13.4 per cent to 9.8 per cent. It is doubtful whether or not this variance has any particular meaning. With regard to the Jewish race, however, it is striking to observe that there were only 3 such in the series, 1 per cent.

RESULTS OF TREATMENT

We have frequently commented upon the fact, as have many others, that freedom from signs and symptoms of cervical carcinoma for a period of five years following treatment is in no sense a criterion of "cure." We have seen recurrence as late as ten years after the initial treatment; for that reason we prefer to use the term "salvage" when speaking of patients who have survived for five years or longer after therapy. On the other hand, as one of us pointed out in a paper presented three years ago,[4] prolongation of life for five years and longer has not infrequently resulted from the successful repetition of irradiation for recurrence.

Our statistics therefore are presented on the following basis:

1. Present-Day Salvage.—a. The number of patients alive following treatment when the observation period is reported, based on the total number of patients actually seen (absolute per cent).

b. The number of patients alive following treatment when the observation period is reported, based on the number of patients actually treated (relative per cent).

2. Five-Year Salvage.—The added number of patients treated during the observation period who have survived for five years or longer but

have eventually died of carcinoma, of an intercurrent condition, or as in some instances, of an entirely different malignant growth (relative five-year per cent). Some patients in this category most certainly do not die of their original carcinoma, but this cannot be definitely stated unless proved with autopsy; hence it is unwise to include such individuals as actually salvaged carcinoma patients, but attention may properly be called to the fact that in this group, a certain number of women presumably did not die as a result of their initial malignancy.

Table IV presents the results secured in the treatment of all patients, irrespective of grouping and embracing all forms of therapy. It will be seen that the absolute salvage is 12.9 per cent; the relative salvage is 13.7 per cent; and the five-year salvage is 23.1 per cent. Five years ago, the percentages were 19.2, 20.5, and 25.3, respectively. Ten years ago the percentages were 14.2, 15.7, and 20.7, respectively. This tends to show that as survivors grow older the mortality rate is influenced by those diseases incident to old age, and not necessarily due to recurrent carcinoma, unless definitely proved. This assumption is borne out by the fact that the five-year salvage figure is relatively constant. Furthermore, some patients who have reacted well to treatment die of intercurrent causes before the five-year observation period has elapsed.

TABLE IV. GENERAL RESULTS OF TREATMENT, ALL GROUPS

Of 293 patients observed, 38 are alive from 5 to 20 years	12.9 per cent (absolute)
Of 277 patients treated, 38 are alive from 5 to 20 years	13.7 per cent (relative)
26 additional patients survived from 5 to 15 years after treatment, establishing a 5-year salvage of	23.1 per cent (relative)
(8 of these 26 patients presumably did not die of carcinoma, and 3 untraced patients were alive 7, 8, and 12 years, respectively, when last seen)	
Primary mortality (4 patients)	1.4 per cent

The percentage of surviving patients who were over 40 years of age when they received their initial treatment is about twice as large as the corresponding percentage of survivors under 40. In other words, the older patients have done twice as well as regards survival as have the younger ones.

Table V shows the results tabulated in percentages, as expressed in Table IV, but arranged to show the results obtained in each group. The results secured in the so-called "early cases" (Groups 1 and 2) are obviously better than those exhibited by the series as a whole, as is to be expected. In Group 1, of 5 patients observed and treated, 2 are alive

TABLE V. RESULTS OF TREATMENT, ALL GROUPS

GROUP	PATIENTS		ALIVE	ABSOLUTE SALVAGE PER CENT	RELATIVE SALVAGE PER CENT	5-YEAR SALVAGE PER CENT
	SEEN	TREATED				
1	5	5	2	40.0	40.0	3—60.0
2	30	30	8	26.6	26.6	13—43.3
3	213	208	26	12.2	12.5	46—22.1
4	25	15	0	0.0	0.0	0— 0.0
5	20	19	2	10.0	9.5	2—10.0
Total	293	277	38	12.9	13.7	64—23.1

10 and 20 years, respectively; an additional patient survived ten years and her death, at the age of 64, was attributed to apoplexy, but there was no autopsy.

Of 30 patients in Group 2 observed and treated, 8 are alive from five to nineteen years. Five additional patients in this group survived from six to twelve years, of whom 4 definitely died of carcinoma, while one is untraced after eight years of good health.

Of the 213 patients in Group 3, 208 were treated and 26 are alive from five to nineteen years. Twenty additional patients survived from six to fifteen years after their initial treatment, of whom 11 are definitely known to have died as a result of cervical carcinoma. Of the remaining 9 patients, 4 were reported to have died of cardiovascular disease at an advanced age, as was a fifth patient, but since she had been operated upon a year before her death for a granulosa cell tumor of the ovary, this pathologic lesion may have been contributory to her death. The sixth patient died of carcinoma of the ovary fifteen years after treatment for carcinoma of the cervix, and at autopsy no trace of carcinoma could be found in the uterus. The seventh patient died of diabetic coma, apparently free of cervical carcinoma. The eighth and ninth patients are untraced but were free of carcinoma when last seen, seven and twelve years after treatment, respectively. Recent investigation leads us to believe that they are still alive, but they have not been definitely located at this writing.

None of the patients in Group 4 survived the five-year period.

In Group 5, two patients were alive eight and ten years after treatment, respectively, out of 20 patients seen and 19 treated.

Four patients died primarily as a result of treatment, a mortality of 1.4 per cent. Autopsy was performed in each case. In two instances, pelvic peritonitis developed promptly, with death occurring on the seventh and tenth postoperative days, respectively. These women were between 40 and 50 years of age and the post-mortem examinations revealed pyogenic processes in the uterus and adnexa in addition to acute suppurative pelvic peritonitis. Radium therapy was undoubtedly the factor in producing or at least activating virulent pelvic infection. The other two deaths occurred in older women, 54 and 64 years of age. One died on the eighth postoperative day, the other on the twenty-first. In neither case was peritonitis found at autopsy. Both exhibited advanced cardiovascular and renal disease in addition to the pelvic findings of advanced carcinoma. Consequently these fatalities could scarcely be ascribed to the radium applications. Specific experience with pelvic peritonitis resultant from radium therapy has been detailed in a previous communication.[5] It may be stated that even the most careful preoperative care and preparation cannot invariably exclude the possibility of the development of postirradiation peritonitis with potential fatality. The part that interstitial irradiation may play in such an outcome is problematical.

TREATMENT WITH SURGERY AND IRRADIATION

Surgery was a factor in the treatment of but 8 patients. Four of these were treated primarily by us, between 1921 and 1923. Immediate panhysterectomy was carried out in 2 patients in Group 1. One was followed with recurrence in the vaginal vault three years later, irradiation with radium and x-ray was successful, and the patient has now sur-

vived for twenty years. The other died nine months later. Two patients in Group 2 received preliminary irradiation with radium, followed by panhysterectomy and subsequent irradiation; one died of recurrence in one and one-half years; the other survived for six years.

Four patients had primary panhysterectomy elsewhere. Their original grouping is problematical, and they were accordingly placed in Group 5. None received preliminary irradiation as far as we know. Three of them treated by us, 2 with radium and one with x-ray for vaginal vault recurrence within a year of the primary operation, survived less than a year. The fourth patient, treated with both radium and x-ray, is now alive eleven years (Table VI).

TABLE VI. TREATMENT, SURGERY AND IRRADIATION, 8 PATIENTS

GROUP	PATIENTS	PRELIMINARY IRRADIATION	OPERATION	SUBSEQUENT IRRADIATION	ALIVE	RELATIVE SALVAGE PER CENT
1	2	1, Yes; 1 No	Comp. hyst.	Yes	1	50
2	2	Yes	Comp. hyst.	Yes	0	0
5	4	No	Comp. hyst.	Yes	1	25
Total	8				2	25

Thus no patient was treated solely by surgery. The very prompt recurrence noted in each instance is mute evidence of the inadequacy of the surgery performed on these patients. It was probably not of the type of which Lynch and Bonney are capable, and serves to stress the point that if a surgical decision is made, it must be carried out by one qualified to perform a truly radical operation based on the premise of an undoubtedly early lesion.

TREATMENT WITH IRRADIATION

Irradiation was used solely in the treatment of 269 patients. The results are tabulated in Table VII, according to groups, contrasting the

TABLE VII. TREATMENT, IRRADIATION ONLY, 269 PATIENTS

GROUP	PATIENTS	ALIVE	REL. SALVAGE PER CENT	5-YEAR SALVAGE	
				PATIENTS	PER CENT
1	3	1	33.3	2	66.6
2	28	8	28.5	12	42.8
3	208	26	12.5	46	22.1
4	15	0	0.0	0	0.0
5	15	1	6.6	1	6.6
Total	269	36	13.3	61	22.6

present-day salvage with five-year salvage. It can readily be seen that these figures are but little altered from those presented in Table V, since the number of patients in whom surgical treatment was combined with irradiation therapy is relatively insignificant.

Of more interest is the manner of employment of irradiation therapy with the results achieved. During the observation period upon which this report is based, treatment underwent several changes. From 1921 to 1931 radium was used principally, most often as a single primary application after the experience of our first year. External irradiation with the x-ray was employed more or less sporadically during this time,

subsequent to the local use of radium, and most often in instances of recurrence. From 1931 to 1934, it was used much more frequently and systematically, subsequent to the radium applications, and as a regular plan of therapy. During this time, too, the x-rays were used more widely in markedly advanced cases with the exclusion of radium. In 1934 and 1935 external irradiation first began to be used as a preliminary procedure and 12 patients were so treated. Ten received x-ray therapy both before and after the use of radium during this time. Since 1936, preliminary external irradiation has been instituted as a routine procedure of choice, and this plan is in vogue at present. Hence this report is based on an observation period of fifteen years, during which radium was generally used primarily and x-ray therapy was utilized afterward as a supplemental factor in the majority of the patients treated.

Table VIII presents the various measures of radiation therapy employed and shows the number of patients treated by each plan, together with the contrasted present-day and five-year salvage. No attempt has been made to indicate the effect of the varying forms of treatment upon each group, since so relatively few patients were in Groups 1 and 2. It will be noted that those patients treated with both radium and x-ray present superior survival rates. It would seem that those patients receiving preliminary irradiation show a higher salvage rate, but it must be remembered that these were the patients who were treated more recently by this method. Only when another five-year observation period has elapsed can we evaluate this newer technique.

TABLE VIII. TYPES OF IRRADIATION TREATMENT AND RESULTS

IRRADIATION	PATIENTS	ALIVE	RELATIVE SALVAGE	SURVIVORS	5-YEAR SALVAGE
Single radium	115	17	14.7%	29	25.2%
Repeated radium	22	2	9.1%	3	13.6%
X-ray only	33	0	0.0%	0	0.0%
X-ray and radium	99	17	17.1%	26	26.2%
Subsequent	77	11	14.2%	19	24.6%
Preliminary	12	4	33.3%	4	33.3%
Both	10	2	20.0%	3	30.0%

We note in Table IX the influence that reirradiation for recurrence has had on the survival rate. Comparison of these figures with our previous report on this subject three years ago shows that at that time 46.2 per cent of our patients then alive from five to sixteen years following initial radiation had survived because of repetition of treatment during the observation period, while the balance of the survivors at that time (53.8 per cent) had received but a single course of therapy. This

TABLE IX. INFLUENCE OF REIRRADIATION

Patients treated, 269; Survivors, 36

22 patients (61.1 per cent)	are alive from 5 to 18 years without evidence of recurrence, following a single course of radiation therapy, a relative salvage of 8.1 per cent
14 patients (38.9 per cent)	survived 5 to 18 years because of reirradiations during the observation period, increasing the relative salvage to 13.3 per cent

lowered trend of ultimate survival in the reirradiated group is readily understandable, when one considers that patients receiving repeated treatments for recurrence are likely to die sooner.

CARCINOMA OF THE CERVICAL STUMP

Among 293 patients, carcinoma of the cervical stump was encountered 14 times, an incidence of 4.7 per cent. This includes all patients seen, irrespective of when the supravaginal hysterectomy had been performed. The time period varied from one to twenty-five years. Four of the patients have survived treatment from eight to fourteen years, a present-day salvage of 28.5 per cent, while 3 additional patients survived six, nine, and eleven years, respectively, a five-year salvage of 50 per cent. Two of the latter patients died of recurrent carcinoma; the third, who survived eleven years, presumably died of cardiovascular disease, but there was no autopsy. This is the same patient who was previously mentioned as having been operated upon a year prior to her death for a granulosa cell tumor of the ovary. Further discussion relating to the problem of cervical stump carcinoma is not pertinent to this report, other than to note the fact that the results of treatment have been better than with carcinoma of the cervix in general. Our views relative to the occurrence and possible avoidance of this condition, together with management, have been expressed in previous presentations[6, 7] (Table X).

TABLE X. CARCINOMA OF CERVICAL STUMP

Carcinoma of cervix		293 patients
Carcinoma of cervical stump		14 patients
Incidence		4.7 per cent
Present-day salvage (8 to 14 years)	4	28.5 per cent
Five-year salvage (6 to 11 years)	7	50.0 per cent

TECHNIQUE OF IRRADIATION

The transition from radium therapy alone to its correlation with external irradiation has been mentioned briefly in a preceding paragraph. The technique, with variations, should be described as a matter of record.

Radium Application.—During the observation period embodied in this report (1921 to 1936), intracervical and interstitial applications were employed, using (1) a 50 mg. capsule of radium, screened with 0.3 mm. of silver and 1.0 mm. of brass, enclosed in black rubber tubing of 2 mm. thickness, and placed in the cervical canal; (2) 8 needles, each containing 12.5 mg. of radium, screened with 0.3 mm. of Monel metal and generally inserted about the periphery of the growth. This combination totaled 150 mg. of radium which was held in position with gauze packing for the time requisite to insure varying dosages. From 1921 to 1924 the average dosage was between 2,000 and 2,200 mg. hr.; from 1924 to 1927, it averaged 3,000 mg. hr.; during 1927 and 1928, the average was 4,300 mg. hr.; from 1928 to 1936 it was decreased to 3,600 mg. hr. because of many severe reactions. Beginning in 1935, an additional 50 mg. capsule, screened with 0.5 mm. of platinum, was obtained to replace the brass capsule or to use in conjunction with it sometimes.

This armamentarium continued in consistent use until early in 1938 when three 50 mg. capsules screened with 1.5 mm. of platinum and ten 10 mg. needles screened with 0.5 mm. of platinum were secured to replace the former equipment. Several more years of observation will have to elapse before we can evaluate what change, if any, has resulted from this alteration in screening.

X-Ray Application.—The late Willis F. Manges and his associates J. T. Farrell, Jr., and R. Manges Smith directed the technique of external irradiation throughout the period of time covered by this report. Since 1938 this phase of the treatment has been supervised by Karl Kornblum and his co-workers.

Prior to 1927 massive doses were given at a single sitting at right angles to one of 3 or 4 pelvic ports. The amount given was that which the skin would tolerate, and the entire course was completed in three or four days. The factors were 3 ma. at 170 to 200 kv., filtered through 0.5 mm. of copper and 1.0 mm. of aluminum at 50 cm. skin-target distance, through ports 16, 19, or 20 cm. square. The total dosage delivered through each port varied from 800 r. to 2,100 r.

After 1927 the fractional method was followed, treatment being directed through 4 ports, 2 anteriorly and 2 posteriorly, with the factors as previously mentioned. The object then was to deliver 100 per cent of the skin erythema dose into the depths of the pelvis in two weeks by giving treatment on alternate days until the saturation level was reached. Treatment was then continued two more weeks. The total dosage delivered through each port by this method varied from 1,400 to 1,500 r. This plan was followed with but little variation throughout the remainder of the observation period.

It was about this time that external irradiation began to be used more or less as a routine procedure prior to the application of radium. In 1938 and 1939, still employing the same factors, multiple portals averaging four in number, two anteriorly and two posteriorly, continue to be employed, cross-firing on the uterus. Two such areas are treated daily, each receiving 200 r. (measured in air). The treatments are continued until a well-marked erythema is obtained which in general will occur with a total of 1,600 to 2,400 r. to each portal, and such a series requires about three weeks for completion.

When we began to use preliminary external irradiation, the radium was applied near the termination of the x-ray treatments or soon afterward. Now the radium application is delayed from two to three weeks, because reactions were sometimes too severe when the internal and external irradiation coincided too closely. There is no doubt that the x-rays diminish local necrosis, slough and infection; pain and bleeding are frequently relieved as well. On the other hand, if too long a time elapses before applying the radium, vaginal vault contractures may occur that render radium insertion difficult. It remains to be seen what the five-year results will be with this present technique, but the present trend of three- and four-year survivals augurs well.

In cooperation with the x-ray department, we are about to initiate transvaginal or so-called cone therapy in conjunction with preliminary external irradiation and the local use of radium. The apparently satisfactory results attained by Behney and others with this method are convincing, and we are eager to institute this feature as a part of our routine.

HISTOLOGIC GRADING AND PROGNOSIS

We have no reason to change our views with regard to the impracticability of attaching prognostic significance to the histologic grading of carcinomatous lesions of the cervix. Radiosensitivity is relative and radiocurability is not an equivalent term. The response to irradiation is not only contingent upon the biologic processes that are constantly going on in all the tissues within range of treatment but also, to an appreciable extent, upon the age and physical status of the patient and the amount of irradiation administered. Consequently it is probable that prognosis depends to a far greater extent upon the clinical characteristics of the lesion and its subsequent response to irradiation than upon primary microscopic gradation. The majority of our surviving patients exhibited lesions of a low or intermediate grade of malignancy and patients with an anaplastic, highly malignant type of tumor cell frequently reacted badly to irradiation. Those with adenocarcinoma did relatively poorly.

COMMENT

Time and space will not permit discussion of numerous interesting problems peculiar to individual patients in this series, occurrences which perhaps are not an uncommon experience in any similar group. Some have been touched upon in passing, as the occurrence of multiple malignancies and the coincidental finding of pelvic inflammatory disease. Granulosa cell tumors of the ovary were removed from 2 patients, ten years after successful radium therapy for cervical carcinoma. Instances of carcinoma developing in cervices that have been subjected to previous repair have occurred and several times malignancy has been discovered by routine cervical biopsy or amputation; coexistence with syphilis is not infrequent. Odd metastases have been observed; annoying bladder and bowel lesions have been seen. Fistulas are known to have occurred in at least 12 per cent of our patients; how many more is problematical as the exact circumstances attending the deaths of patients in remote areas are not always clear. The list could be prolonged; much material is available for further associated investigation.

An intimate study such as this, pursued over a period of twenty years, is bound to be discouraging in view of the low survival rate presented. The personal contact with so many hopelessly ill patients, and with their grieving relatives and friends creates impressions that can never be erased. When experience tells us that one out of four or five patients will perhaps remain well for five years or more, and that if we follow such survivors sufficiently long, death from recurrent carcinoma will eventually claim half of them, it cannot leave one lighthearted. Year after year we see the same large group of women coming to us with far-advanced disease because so often ignorance and indifference have resulted in late diagnosis, this in spite of vigorous cam-

paigns to spread the knowledge required to insure an early diagnosis and the institution of effective treatment.

But there is the brighter side, the supreme satisfaction that comes with seeing those who improve and remain well. It is these successes that keep alive that spark of effort, which induce us to go on and on, constantly trying to improve our methods, not only by seeking new departures in treatment, but by analyzing and profiting by the failures of the past.

SUMMARY

1. An analysis of a series of 293 patients with carcinoma of the cervix observed on the Gynecological Ward Service, Jefferson Medical College Hospital, from Sept. 1, 1921, to Sept. 1, 1936, of whom 277 were treated, is presented, based upon a follow-up study of 97.2 per cent of the patients seen and of 97.8 per cent of those treated.

2. An absolute present-day salvage rate of 12.9 per cent, a relative present-day salvage rate of 13.7 per cent, and a relative five-year salvage rate of 23.1 per cent are presented. These are contrasted with rates of 19.2 per cent, 20.5 per cent, and 25.3 per cent respectively, published in 1936; and with rates of 14.2 per cent, 15.0 per cent, and 20.7 per cent respectively, published in 1931.

3. Various phases of the analysis are discussed and compared with the previous reports, together with the exhibition of pertinent data.

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DISCUSSION

DR. CHARLES A. BEHNEY.—This paper represents more than twenty years of work by one individual, a unique series in which comparisons are of greater value than when the observations of various persons are recorded.

The extent of involvement in Dr. Scheffey's group of patients is fairly typical of similar series in the average hospital. One series which varies materially from it is that from the Woman's Medical College Hospital, with its astonishingly large proportion of cases in Groups 1 and 2. I have always suspected that these latter figures were less the result of the routine examinations of apparently healthy women, than the outcome of years of persistent teaching by Dr. Macfarlane and her associates, of hundreds of students in the importance of routine pelvic examinations and frequent biopsy. These after graduation searched diligently for early lesions of cancer, which when found were promptly referred to the Woman's Medical College for treatment.

At the end of five years, 23.1 per cent of patients were living and free of symptoms of cancer. Fifteen years later, only 12.9 per cent were still well, a deterioration in results amounting to about 44 per cent. Several years ago Kimbrough and Tompkins studied the records of the gynecologic service of the University Hospital, to compare the ten-year salvage of carcinoma of the cervix, with that at the end of five years. They found that in the second semidecade, 17 per cent of the patients who had been well after five years died of carcinoma or some other disease. Likewise, in the series of Ward and Sackett, there was a 27 per cent loss, and in Lynch's series, one of 17 per cent in the second five years after treatment. Bonney reports a decrease of 23 per cent in his salvage, five to ten years after *radical hysterectomy* for carcinoma of the cervix. It would be very interesting and enlightening, if ten- to twenty-year results in Grade 1, 2, 3, and 4, respectively, could be compared. It would be logical to find less deterioration in the statistics of Grades 1 and 2 than in those more advanced, since dissemination would be less probable before treatment was applied.

It is obvious that a woman who had been afflicted with carcinoma of the cervix, and who is well five years after being treated, cannot be guaranteed freedom from subsequent recurrences. Yet, I doubt whether in a series of patients of a similar age, suffering from coronary disease, cerebral hemorrhage, nephritis, etc., any method of treatment will permit 25 per cent to be free from symptoms five years after treatment. The patient who had cancer of the cervix, furthermore, can enjoy a comparatively unrestricted life during this five-year period. This point should lend a more cheerful aspect to cancer of the cervix, and if more generally known, should remove some the prevalent horror for this disease.

DR. CATHARINE MACFARLANE.—Knowing the difficulty of keeping in touch with ambulatory patients in a large city, I was particularly impressed with the fact that Dr. Scheffey has been able to follow-up 97.8 per cent of his cases. This demonstrates the enthusiasm of the Department of Gynecology of Jefferson Medical College and the efficiency of that Hospital's Social Service Department as well.

The fact that less than 12 per cent of Dr. Scheffey's patients were in Groups 1 and 2 of the Schmitz classification, once more calls attention to the tragic delay which elapses in so many of these cases between the first symptom and adequate treatment. It once more raises the question of the responsibility for this delay. In a series of 83 cases of cancer of the cervix admitted to the gynecological service of the Hospital of the Woman's Medical College, the delay period ranged from three days to five years. The average is approximately eleven months. A study of the records of these cases revealed the fact that in 77 per cent the delay was due to the *patient's* ignorance, indifference or fear, while in 23 per cent the responsibility for the delay rested upon the family physician. Prescribing without examining, examining without inspecting the cervix, failure to make a biopsy, lack of a good pathologist were the chief factors in the physician's delay. It would seem that these factors were preventable.

After watching the success attending the efforts of the Committee on Maternal Mortality of the Philadelphia County Medical Society, under Dr. Philip Williams' leadership, I have felt for a long time that a similar committee devoted to the study of the delay period in cancer of the uterine cervix might accomplish a great deal to eliminate the element of physicians' delay in these cases.

Further study of Dr. Scheffey's paper reveals the fact that in 115 patients receiving a single radium treatment, the five-year salvage was 25.2 per cent, whereas in 99 patients receiving both x-ray and radium, the five-year salvage was 26.2 per cent. The close similarity of these percentages raises the question as to whether or not the x-ray plays an essential role in the treatment of cancer of the cervix. It would be interesting to have these cases analyzed according to the stage of the disease

present. It would also be interesting to compare Dr. Scheffey's statistics in this respect with those of other large clinics. In view of the fact that in the Hospital of the Woman's Medical College we invariably use both radium and x-ray, I am not in a position to express an opinion.

DR. GEORGE LAWS.—Will Dr. Scheffey tell us how many cases of carcinoma of the cervix passed through the large clinic in the Jefferson Hospital and did not go into the ward and how many early cases were picked up at the clinic? In our work we have been limited in our treatment of patients with the advanced disease. After failing to cure them, we are not able to continue to treat them on account of lack of facilities.

DR. SCHEFFEY (closing).—Dr. Macfarlane's suggestion regarding the formation of a committee to reduce the mortality from cervical carcinoma, along the lines of the work that has been accomplished in the field of maternal mortality, is indeed a valuable one and worthy of further thought.

My impression is that the results obtained during the past four or five years, which of course do not influence the present report, will show improvement, since external irradiation with x-ray has preceded local radium applications. It was only during the last year or so of this report that such a technique was employed more or less routinely. It seems to me that the present three- and four-year survivals indicate a more hopeful trend.

What I especially wanted to point out tonight was: First, the number of patients now alive from five to twenty years after treatment; second, the additional number who survived treatment for five years or more, but had eventually died either from recurrent or unarrested carcinoma, or from some intercurrent disease. In the latter instance, in the absence of an autopsy, we have classified these deaths as due to carcinoma even though such a presumption may not have been correct. On this basis the five-year salvage has remained more or less constant, ranging from 22 to 25 per cent throughout the observation period.

Dr. Behney has referred to the findings of Kimbrough and Tompkins, who compared the salvage at the expiration of five- and ten-year periods. It so happens that I discussed that paper, and our results closely approximated theirs: 18.8 per cent of the patients who had been well after five years died thereafter of carcinoma or of an intercurrent condition.

In answer to Dr. Laws I would say that our patients reach the gynecologic service either by direct reference to the hospital or through the out-patient department. If other arrangements can be made, we try not to admit hopelessly ill patients (Group 4). With an active but limited service of 27 beds, such a policy is necessary, but we take care of every patient that we think can be helped. Others must be sent to institutions designed to provide care for incurable cases of any sort, and this is not infrequently resorted to with patients who have received the maximum treatment that we have been able to provide for them without avail.

THE CONTRACTIONS OF THE HUMAN UTERUS DURING PREGNANCY AND LABOR*

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RECENT studies of the motility of the nongravid human uterus have revealed the presence of a cycle of myometrial activity under the control of the ovarian hormones.[1-3] The contractions in the follicular phase of the menstrual cycle are characterized by small amplitude, short duration, short intervals between contractions, and high tonus. In the luteal phase, which follows ovulation, the contractions gradually increase in amplitude and duration but decrease in frequency and tonus. The maximum amplitude is reached as a rule at the onset of menstruation after which there is a gradual return of the small waves. This cycle has been reproduced in castrates by administering the ovarian hormones in the natural sequence: first estrogen alone and then together with progesterone.[4] The possibility that the change from the follicular to the luteal phase contractions represents a *progravid* phenomenon, analogous to the secretory transformation of the endometrium, stimulated this study of the motor activity of the uterus during pregnancy and labor, which was begun in October, 1939.

The misconception has arisen in some quarters that the uterus, under the alleged inhibitory influence of progesterone, remains quiescent during pregnancy. While this may be the case in the rabbit, as claimed by Knaus, Reynolds and others, the evidence is conclusive that progesterone† augments the contractility of the human uterus.[2-4] Braxton Hicks,[5] in 1871, demonstrated by abdominal and vaginal palpation that the human uterus undergoes spontaneous intermittent contractions throughout pregnancy. Schatz,[6] in the following year, published the first records of labor pains obtained by means of an intrauterine bag. This method has since been used successfully by a number of workers in studying the effects of drugs on the puerperal uterus. The bag, however, is not a practical means of recording the contractions of the pregnant uterus because of the danger of abortion and infection. Technical

*Read at a meeting of the New York Academy of Medicine, Section of Obstetrics and Gynecology, November 25, 1941.

†More accurately, progesterone in the absence of estrogen has little if any effect on the human uterus.[4] It is the combined action of progesterone and estrogen that stimulates myometrial activity. Since the corpus luteum and the placenta produce both hormones simultaneously, pure progesterone effects can occur only under experimental conditions in castrates.

difficulties also arise in maintaining sufficient pressure within the balloon probably due to the extreme distensibility of the gravid uterus.

The first attempt at external hysterography was made by Schaeffer[7] in 1896, but his apparatus was too cumbersome. Rübsamen,[8] in 1920, introduced a second method which, while ingenious, was inaccurate in use. The first dependable apparatus for external hysterography was designed by Dodek[9] in 1932 in connection with a study of the action of drugs and anesthetics on the parturient uterus. Since then a number of modifications of his technique have appeared.[10-13] Most of the present external methods are based on the principle that the contraction of the uterus results in a forward displacement of the anterior abdominal wall. The degree of displacement can be measured by placing a suitable tambour, usually pneumatic or mechanical, in contact with the abdomen in the region of the umbilicus. Fenning[14] has recently perfected an extremely sensitive electrical method of recording the abdominal wall movements.

MATERIALS AND METHODS

The abdominal tambour employed in this study is of the pneumatic type and is essentially an inexpensive and simplified modification of the Dodek apparatus. It has proved to be highly sensitive and very satisfactory in use. The details of the set-up are shown in Fig. 1. A total of 283 recordings were obtained from 81 patients, white and colored, ranging in age from 16 to 40 years, who were attending the prenatal clinics or residing on the obstetric wards of the Morrisania City Hospital. Both normal and abnormal cases of pregnancy and labor were included. The greatest number of tracings from a single patient was 23, the least one. Thirty women were pregnant for the first time; the remaining 51 patients had from 1 to 14 previous pregnancies.

In some patients weekly observations were made throughout pregnancy, beginning with the third month when the uterus had risen sufficiently above the symphysis to make contact with the abdominal tambour. In other cases, daily recordings were made at various stages of pregnancy for one or more weeks. Tracings were also obtained from women in labor, term, and premature, and from women in whom labor was being induced by various means (castor oil, quinine and pituitrin, stilbestrol, pregneninolone, rupture of the membranes, and bougies). The indications for the inductions were toxemia of pregnancy, post-term pregnancy, premature rupture of the membranes and heart disease. One case of hydatid mole was also studied. A few observations were made in the early puerperium, but contractions were rarely recorded after the fifth day because of uterine involution. The recordings were made for a minimum of thirty minutes with the patient lying quietly but comfortably in bed. Most tracings ran for one hour and in some cases as much as three hours.

RESULTS

The results of this study will be presented by describing several typical cases which illustrate the important features.

ECTOPIC PREGNANCY

CASE 1.—M. H., white, 38 years of age, para ii, entered the Vanderbilt Clinic* for primary dysmenorrhea. Menses previously were regular every twenty-eight days. The last period, however, began Feb. 5, 1940. Pelvic examination on May 2, 1940, failed to reveal any signs of pregnancy. The following kymographic records were made with an intrauterine balloon: Fig. 2, *A* (May 2, 1940) showed the presence of minute

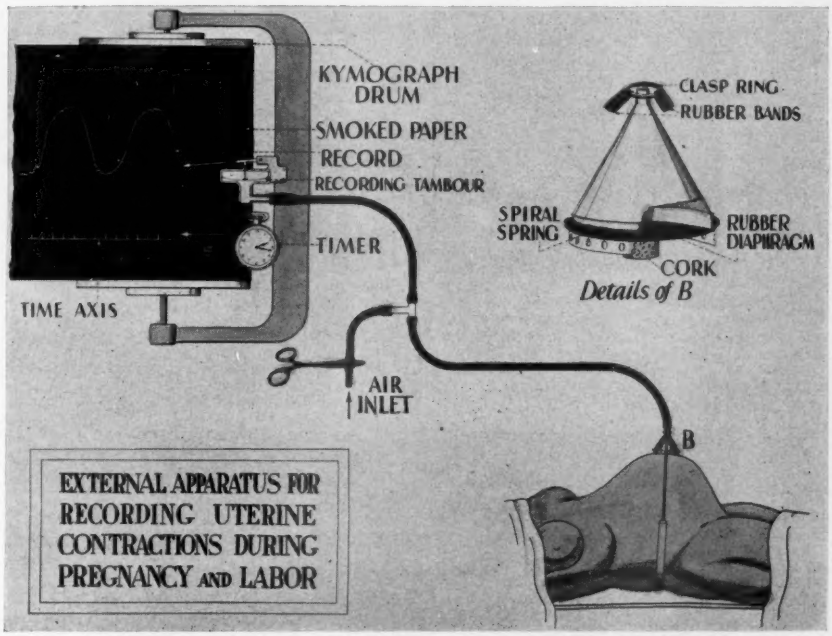

Fig. 1.—The abdominal tambour consists of an aluminum funnel, 2½ inches in diameter at its base, which is covered by rubber tissue to form a diaphragm. A leakproof attachment of the diaphragm is secured by cementing it to a tightly-fitting, rubber-covered spiral spring (used in contraceptive pessaries) around the base of the funnel. Direct contact of the diaphragm with the skin is avoided by interposing a perforated metal band. Contact is made by means of a cork cemented to the diaphragm. If this were not done, perspiration would make the diaphragm adhere to the skin and the body heat would raise the air pressure in the conducting system. The abdominal tambour is held in place by means of a canvas belt and stout rubber bands which hook on to a clasp ring at the neck of the funnel. Pressure tubing connects the abdominal and recording tambours, but a T-tube is interposed to permit adjustment of the pressure. The T-tube is clamped in an interval between contractions (determined by palpation).

barely discernible waves. The balloon pressure was low (40 mm. of mercury) despite the introduction of an additional volume of air. We now recognize these findings as being characteristic of early gestation. Fig. 2, *B* (May 16) and *C* (May 20) revealed a similar picture but the intramuscular injection of pituitrin (20 I.U.) evoked a prompt tonus rise and the appearance of moderate size contractions. Fig. 2, *D* (May 23) showed large prolonged contractions of the type usually seen a few days preceding and during menstruation. The patient now complained of mild abdominal pains and slight vaginal bleeding. These

*I am indebted to Professor Benjamin P. Watson for permission to include this case.

symptoms suddenly became markedly aggravated on May 26, 1940. Laparotomy two days later disclosed a ruptured left tubal pregnancy. The uterus was slightly enlarged; a small fetus, placenta, old and recent blood clots were found free in the peritoneal cavity.

The exact time of rupture was uncertain, but from analysis of the clinical and pathologic pictures, it is probable that a mild rupture occurred some time between May 20 and 23, and a second but more ex-

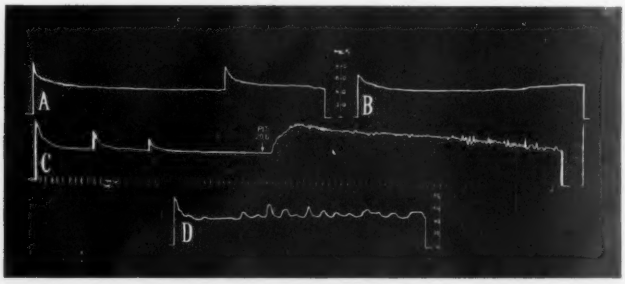

Fig. 2.—(Case 1.) Contractions recorded by intrauterine balloon in a case of tubal gestation. *A*, *B*, and *C* before rupture reveal practically no contraction waves and low pressure which is not increased by introduction of additional air because of extreme distensibility of uterus. Pituitrin, however, produces increased tonus and moderate size contractions (*C*). Following rupture large uterine contractions are recorded without use of pituitrin (*D*). Time intervals indicated in minutes.

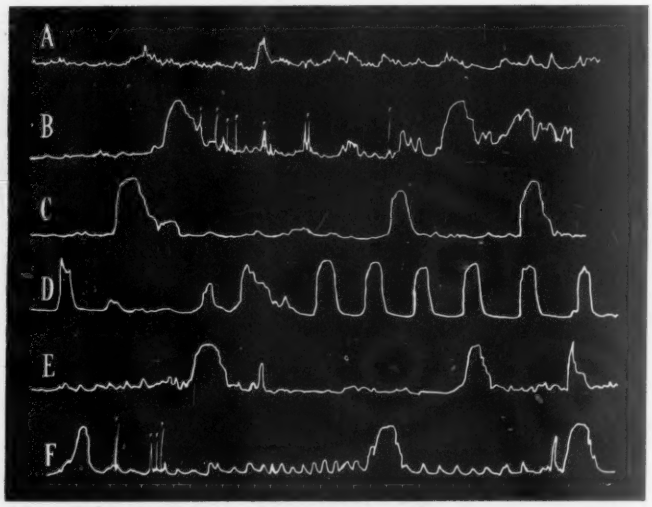

Fig. 3.—(Case 2.) Uterine contractions recorded by external hysterography at monthly intervals during a normal pregnancy. *A*, Third month; *B*, fourth month; *C*, fifth month; *D*, sixth month; *E*, seventh month; *F*, eighth month. Note totally arrhythmic pattern of motility during pregnancy. Two types of contraction waves are present: (1) large prolonged waves (Braxton Hicks contractions) and (2) small waves of short duration. Sharp vertical thrusts (*F*) are caused by fetal movements. Time intervals indicated in minutes.

tensive rupture took place on May 26 when the symptoms suddenly became acute. The registration of the large contractions for the first time in Fig. 2, *D* is accounted for by the diminished uterine distensibility following the disturbance of the gestation. Prior to the tubal rupture uterine contractions were recorded only after the administration of

pituitrin. It is evident that the intrauterine balloon is not a satisfactory method of hysterography during gestation.

NORMAL PREGNANCY

CASE 2.—M. T., white, 26 years of age, had one previous full-term pregnancy. Expected date of confinement June 10, 1940. The following series of tracings were made by external hysterography at monthly intervals during the major portion of an uncomplicated pregnancy: Fig. 3, *A* (Dec. 15, 1939) during the third month, *B* (Jan. 19, 1940) fourth month, *C* (Feb. 14, 1940) fifth month, *D* (March 13, 1940) sixth month, *E* (April 24, 1940) seventh month, and *F* (May 15, 1940) eighth month. Delivery occurred spontaneously on June 4 after a six-hour labor.

This series, which is typical, demonstrates that the human uterus normally contracts in a totally arrhythmic fashion throughout pregnancy. There are two types of contraction waves:

1. Large prolonged arrhythmic waves of one to five minutes' duration which are easily palpated and are often perceptible to the patient as a cramplike sensation or pain (false labor pains). These are the Braxton Hicks contractions. They probably represent mass contractions in which all the uterine muscle fibers participate. At times these large arrhythmic waves occur at frequent intervals and rarely they may be absent in a two-hour period of observation.

2. Small arrhythmic waves not exceeding one minute in duration. They are seldom present during normal labor, cannot be palpated, and are rarely noted subjectively. They were only recently described by Douglas Murphy[15] and may represent regional myometrial activity.

Periodic variations in contractility corresponding to the time of menstruation (if pregnancy did not exist) have not been observed. Nor has any progressive increase in myometrial activity been noted as gestation advanced. The contractions throughout pregnancy are totally irregular.

INDUCED PREMATURE LABOR

CASE 3.—D. M., white, aged 33 years, a multipara, was hospitalized because her pregnancy was complicated by chronic nephritis. A series of daily tracings (Fig. 4) was obtained during a twelve-day period preceding induction of premature labor. The last menstrual period began July 15, 1939, and the date of expectancy was April 22, 1940. The first tracing was obtained on March 3, 1940. Labor was induced March 14 during the thirty-fifth week of gestation by the oral administration of 100 mg. of stilbestrol in 5 divided doses at hourly intervals followed by castor oil, quinine, and pituitrin. Labor began after the fourth dose of pituitrin and terminated spontaneously eight hours later in the birth of a living premature infant.

This group of tracings demonstrates the rather abrupt change from the markedly irregular contractions of pregnancy to the rhythmic pattern of motility in labor. The contractions shown in Fig. 4, *L*, which were recorded a few hours preceding the induction, occurred regularly at eight-minute intervals and were painless. Rhythmicity, however, is

not an invariable forerunner of labor. For example, Fig. 3, *D* showed a group of 6 contractions occurring at two-and-one-half-minute intervals but this rhythmic activity was not maintained, and labor did not start until eleven weeks later.

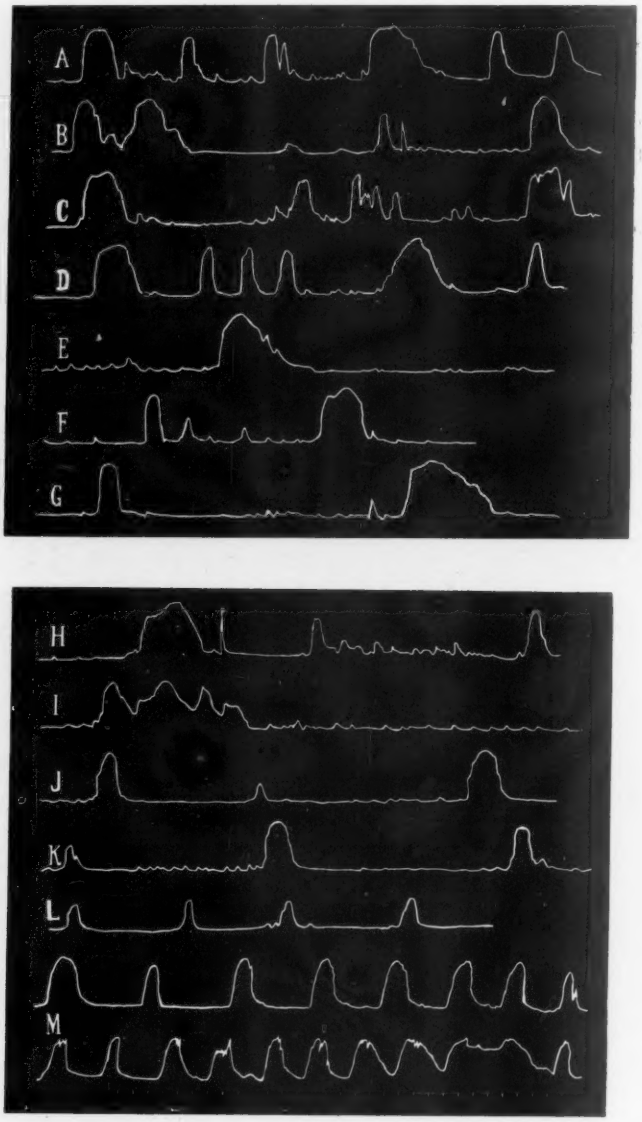

Fig. 4.—(Case 3.) Daily tracings during eighth month of pregnancy beginning twelve days before the induction of premature labor for chronic nephritis. Totally arrhythmic pattern of contraction with painless large and small waves before labor (*A-L*). During labor (*M*) all contractions are large, painful and rhythmic. Spontaneous delivery occurred ten minutes after end of tracing.

What do these transient episodes of rhythmic myometrial activity during pregnancy signify? It would seem that they represent attempts by the uterus to evacuate its contents. It is well known that the uterus

is capable of expelling the fetus at any stage of gestation. Why it usually does not before term is reached is not known, but it may be assumed that some additional factor is necessary either to release the energy of the uterus or more likely to give it the extra stimulus it may require. These rhythmic episodes bear a striking resemblance to the contractions that follow the administration of pituitrin (Fig. 5, *C*). The role of the posterior pituitary in initiating parturition has received scant consideration, since it was demonstrated that labor can occur in hypophysectomized animals. Recent evidence, however, points to the

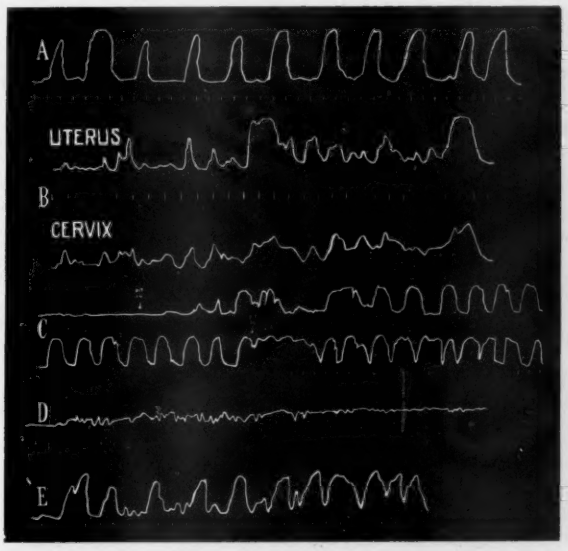

Fig. 5.—*A* (Case 4), reveals large rhythmic contractions in labor at term. *B* (Case 5), is a simultaneous recording of uterine contractions and the changes in the position of the cervix during the thirty-first week of pregnancy. Note that the cervix is retracted or pulled up with each contraction. Retraction during pregnancy leads to important preparatory changes for labor. *C* (Case 6), demonstrates clonic and tetanic contractions induced by pituitrin in a multipara near term. Note similarity of clonic contractions to labor pains. *D* (Case 7), reveals small, frequent arrhythmic contractions in a case of uterine inertia during labor. Large contractions absent. *E* (Case 8), demonstrates the typically arrhythmic large and small pregnancy contractions in a case of hydatidiform mole.

probability that oxytocic substances are produced in other parts of the brain,[16] and it may therefore be necessary to reconsider this hypothesis which has much to recommend it.

NORMAL TERM LABOR

CASE 4.—E. S., white, aged 39 years, a multipara at term, was in labor. Fig. 5, *A* reveals the uterine contractions seven hours after the spontaneous onset of labor. The membranes were intact and the cervix was 2 fingers dilated. The pains were fairly regular and occurred at approximately four-minute intervals. Spontaneous delivery took place three hours later. The appearance of these rhythmic contractions is the same whether labor occurs at term, past term, or prematurely, and whether it begins spontaneously or is induced.

THE RELATION OF THE CERVIX TO THE CONTRACTIONS OF THE UTERUS

CASE 5.—D. M., white, 33 years of age, a multipara, was thirty-one weeks pregnant. Fig. 5, *B* is a simultaneous record of the contractions of the uterus and the changes in the position of the cervix. The cervical movements were registered by leading a silk thread sutured at one end to the cervix through a pulley arrangement to a muscle lever writing on the smoked drum. It will be noted that the cervix was retracted or pulled up with each uterine contraction and that it dropped down when the uterus relaxed. This phenomenon was recorded as early as the twentieth week of gestation and was seen during the remainder of pregnancy, labor, and the early puerperium.

What is the function or purpose of the Braxton Hicks contractions? Braxton Hicks himself suggested that they aid the circulation of blood through the uterine and placental sinuses and assist in adapting the position of the fetus to the form of the uterus.[5] There also can be no question but that a muscular organ, if it is to grow and maintain its tone, must contract. An additional and extremely important function appears to be concerned with the changes that occur in the arrangement of the muscular elements of the uterus during the course of pregnancy. These changes, which are essential preparations for labor, include the division of the uterus into upper and lower segments, some degree of cervical effacement, and in some women (particularly multiparas) partial dilatation of the cervix.[17-19]

RESPONSE TO PITUITRIN

CASE 6.—M. S., white, 39 years of age, a multipara, entered the hospital at term with false labor pains which soon subsided. Fig. 5, *C* is a tracing taken during the course of an unsuccessful Watson induction and is presented to demonstrate the effects of pituitrin on the pregnant uterus. During the control period of ten minutes, there was little myometrial activity. Clonic contractions appeared soon after the subcutaneous injection of 1 I.U. of pituitrin and continued at fairly regular intervals for about fifty minutes when a second injection of 2 I.U. was given. This was followed almost immediately by a tetanic contraction of five minutes' duration. The clonic contractions then reappeared but did not persist. The patient was sent home and returned to the hospital two weeks later when the membranes ruptured. Labor began spontaneously and terminated thirty minutes later in the birth of an 8-pound infant.

According to Murphy there is a significant relation between the response to pituitrin administered during late pregnancy and the length of labor.[20] He also noted that the response to pituitrin occurred more often (a) in multigravidas than primigravidas, (b) during than before labor, (c) later in pregnancy than earlier, (d) after larger than smaller doses of pituitary extract, and (e) when the uterine wall was tense than when it was relaxed.[21]

UTERINE INERTIA AND THE EFFECT OF ANALGESIA

CASE 7.—H. F., white, 21 years of age, a primigravida, entered the hospital eleven days past the expected date of confinement with mild infrequent labor pains and ruptured membranes of twenty-four hours' duration. The pains soon increased in frequency and intensity. Analgesia in the form of morphine sulfate (gr. $\frac{1}{6}$) and scopolamine hydrobromide (gr. $\frac{1}{150}$) was administered by subcutaneous injection. The pains ceased shortly afterwards. Fig. 5, *D* is a tracing taken twelve hours after the analgesia was given. The cervix was now two fingers dilated. The tracing reveals the presence of small, frequent, arrhythmic contractions of short duration. Typical labor contractions are absent. The pains returned 4 hours later following a hot enema and continued at regular intervals for 10 hours when spontaneous delivery occurred.

The effect of analgesia administered during labor is often unpredictible. In some instances the contractions increase in frequency and intensity and precipitate delivery may occur. In other cases there is no effect on the contractions.

HYDATIDIFORM MOLE

CASE 8.—E. L., a 42-year-old white woman, was admitted to the hospital with a history of amenorrhea of eight months' duration. The uterus, however, was the size of a six months' gestation. Fetal heart sounds, movements, and parts were absent. One-tenth cubic centimeter of urine gave a strongly positive Friedman test. External hysterography revealed the presence of both the large and small contractions occurring in the characteristically irregular pattern of pregnancy (Fig. 5, *E*). A hydatidiform mole was later removed by abdominal hysterotomy. It is interesting to note that Braxton Hicks had recognized the presence of contractions in this condition.[5]

CONCLUSIONS

Pregnancy, aside from the development of the fertilized ovum, is merely a continuation of the luteal phase of the menstrual cycle. The same hormones (estrogen and progesterone) are produced by the corpus luteum and the placenta, and the same irregular type of myometrial activity takes place. Apparently the arrhythmic contractions of pregnancy gradually bring about a division of the uterus into an upper and a lower segment and some degree of effacement and dilatation of the cervix. These preparatory steps in the expulsion of the fetus are rapidly completed by the rhythmic contractions of labor whose appearance is rather abrupt. Labor may be regarded as the terminal event of a process designed to expel the products of gestation that begins at the time the ovum is fertilized. Just what it is that usually prevents premature emptying of the uterus is still a question. When this is known we may understand the cause of the onset of labor.

Grateful acknowledgment is given to Dr. Harry Aranow, Director of Obstetrics of Morrisania City Hospital, for permission to conduct this study and to Professors Charles C. Lieb and Michael Mulinos of the Department of Pharmacology, College of Physicians and Surgeons, Columbia University who have generously provided the necessary equipment and many helpful suggestions. The posterior pituitary solution used in this study was supplied by E. R. Squibb & Sons through the courtesy of Dr. J. A. Morrell.

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Warren, Shields: The Relation of Chronic Mastitis to Carcinoma of the Breast, Surg., Gynec. & Obst. **71**: 257, 1940.

The development of breast cancer in 1,206 women, whose breasts had been operated upon for benign noninfectious lesions of the breast, was studied and compared with the incidence of breast cancer in females of the general population in the same age groups.

While the data are insufficient with regard to adenoma and adenocystoma, they do indicate that adenoma is without significance as regards subsequent malignancy, and that adenocystoma is a precancerous lesion.

When age specific rates are used, the breast cancer attack rate for women with chronic mastitis and related lesions in the age group from 30 to 49 years is 11.7 times the rate for the Massachusetts female population; in the group over 50 years of age, 2.5 times as great; in the entire group, 4.5 times as great.

Chronic cystic mastitis and chronic mastitis predispose to the development of breast cancer. No means at present exist to determine those lesions which will develop cancer and which will not. The risk is not sufficiently great to warrant bilateral mastectomy in cases of chronic mastitis and chronic cystic mastitis.

Patients in whom these lesions are found on operation should subsequently be carefully watched and simple mastectomy done if nodules or cysts develop in residual breast tissue.

William C. Henske.

THE COMPARATIVE PHYSIOLOGY OF PLACENTAL TRANSFER

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THE questions concerned with placental permeability or placental transfer which have, until recently, been put to experimental test, are very largely concerned with the problem of whether a particular substance will pass through the placenta. These substances vary from metabolites[1, 2] and hormones[3, 4] of obvious and important interest to fetal physiology, to molecules supposedly of graded size used to estimate the limit of placental permeability.[5] A few of these studies have been performed with the concept of comparative physiology in mind; the importance of this approach rests in the wide differences found in the histologic structure of the placenta in different species of animals. The conclusion to be drawn from such studies is that the placentas which morphologically appear less permeable are in fact less permeable when tested physiologically. Thus, for example, antibodies pass the human placenta, which is hemochorial, but not the syndesmochorial placenta of the cow.[6, 7]

An important step was taken by Lell, Liber, and Snyder[8] who proposed, by studying the rate of transfer of phenolsulfonphthalein from fetus to mother, to investigate possible changes which might take place in the rate of placental transmission at various parts of gestation in the rabbit. A similar step was later taken by Rodolfo[9] in an effort to measure changes in permeability of the placenta to antibodies at different parts of pregnancy. Both sets of data lead to the conclusion that the rabbit placenta of late pregnancy is more permeable than that of early pregnancy.

Before the principles underlying placental transfer can be well understood, the following questions must be answered. Does the permeability of the placenta vary with the period of gestation? If the answer be positive, what are the underlying causes for the variation? Are there differences in permeability among the several morphologic types of placentas? Is the quantity of substance transferred across the placenta related to the rate at which the fetus is growing? Does the placenta act as an inert membrane or filter placed between the maternal and fetal circulations or does it modify the transmission of substances by contributing energy to the process and so acting as an organ of secretion? How is the failure of a substance to pass the placenta related to its physical and chemical characteristics? What effects do pathologic

processes have upon placental transmission and so upon the nutrition of the fetus?

Ideally, from an experimental standpoint, one should be in a position to study the problems with several or many test substances; and these substances should be as closely related as possible to those molecules which normally pass the placenta. The advent and development of stable and radioactive isotopes, together with reliable methods of exquisite sensitivity for their detection, has furnished a method which satisfies this criterion. The isotope may be used to identify or "mark" a molecule (e.g., heavy hydrogen of atomic weight 2 replaces its isotope, hydrogen of atomic weight 1, in heavy water) and the molecule subsequently traced by detecting the isotope. Or the isotope may be studied directly as an ion (e.g., Na^{24} which is radioactive and which is detected by an instrument used for measuring radioactivity).

The present paper brings together the results of several separate investigations on the comparative physiology of the placental transfer of radioactive sodium. This substance was chosen as the beginning tracer material, because it is easily prepared by the cyclotron or electrostatic-pressure generator, its behavior in the body is not complex, and it is one of the physiologically important chemical building stones of the organism. In all instances, it has been used in a concentration far below the toxic level.[10]

The details of the experimental procedure may be found in the original communications.[11-16] Suffice it here to say that the essential steps were, (a) intravenous injection of the radioactive sample into the mother, (b) removal of the fetus by abdominal hysterotomy at a known interval, about an hour, after the injection, (c) measurement of the placental weight and fetal weight, (d) measurement of the radioactivity present in the ashed remains of the fetus and in a sample of maternal blood plasma.

The data from the various observations on the guinea pig, rat, rabbit, cat, goat, and sow have yielded the following correlations: (1) correlation of rate of transfer across a unit weight of placenta with the period of gestation, (2) correlation of transfer rate across the placenta with respect to morphologic type of placenta, (3) correlation of change in transfer rate to fetus with variation of relative growth rate of fetus. These correlations will now be discussed separately; the details of the observations may be found in the original communications.[11-16]

1. *Variation of the Rate of Transfer Across a Unit Weight of Placenta With the Period of Gestation.*—The transfer rate per unit weight of placenta is obtained for a particular period of gestation by calculating the amount of sodium transferred to the total fetus in a known period of time and dividing this quantity by the weight of the placenta.

The results of the observations on the six animals which have been studied are given in Fig. 1. To represent all of them on a common chart,

it has been necessary to plot, at fractional parts of the gestation period, the transfer rate per unit weight of placenta in terms of the maximum rate which is observed near term. This is obviously required because, among the several animals, there are wide differences both in length of gestation period and magnitude of placental rates.

The amount of sodium (Na) supplied to the fetus in a unit time can be obtained readily from the quantity of radioactive sodium (Na^{24}) found in the fetal ash and maternal plasma. The Na^{24} present in the maternal circulation is thoroughly mixed with all the Na of the maternal plasma. Any Na^{24} which passes from the mother to the fetus is accompanied by Na from the mother and in the same proportion as holds for the maternal plasma since the two isotopes, in this regard, behave equiva-

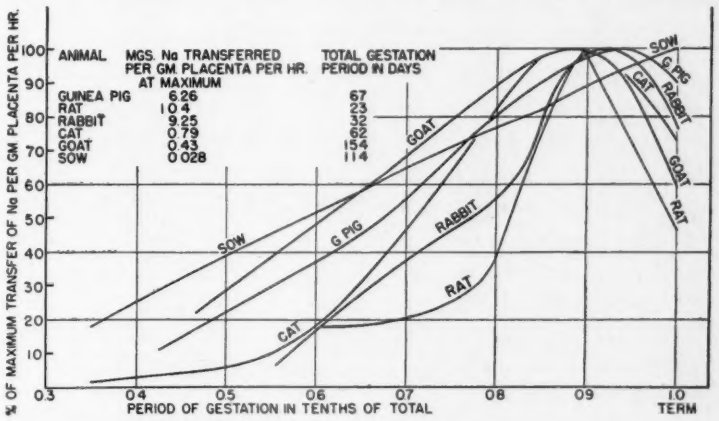

Fig. 1.—Variation of rate of transfer of sodium across unit weights of the indicated placentas with the period of gestation. As explained in the text, the actual quantity of sodium which is transferred across a gram of placenta can be calculated from the data of the figure for any day of gestation.

lently. If the concentrations of Na and Na^{24} in the maternal plasma be designated, respectively, by $Na_{M.P.}$ and $Na^{24}{}_{M.P.}$, and the total Na and total Na^{24} transported to the fetus per hour by $Na_{T.F.}$ and $Na^{24}{}_{T.F.}$, then:

$$\frac{Na_{T.F.}}{Na^{24}{}_{T.F.}} = \frac{Na_{M.P.}}{Na^{24}{}_{M.P.}}$$

Hence

$$Na_{T.F.} = \frac{Na_{M.P.}}{Na^{24}{}_{M.P.}} \times Na^{24}{}_{T.F.}$$

The concentration of Na in the maternal plasma has been assumed to be 3.3 mg. per c.c. in each instance. The actual amount of sodium passing across a unit weight of placenta on a particular day of gestation can be readily found with the values read from the graph together with values presented in the table of Fig. 1. For example, suppose one wishes to know the transfer rate per gram placenta in the case of the rabbit at the twenty-third day of gestation. The total gestation period in the rabbit is thirty-two days. The twenty-third day, consequently, is 0.72

of the total gestation period. The transfer rate at this time, as is evident from the graph, is 41 per cent of the observed maximum, and this maximum, as is to be seen in the table, has a value of 9.25 mg. of sodium per gram placenta per hour. Hence, each gram of the rabbit's placenta on the twenty-third day of pregnancy transfers 3.8 mg. Na per hour.

Fig. 1 shows that the six placentas all have the common characteristics of an increase in transfer rate as pregnancy proceeds. So far as the data are concerned, this change is most pronounced in the cat. A unit weight of the cat's placenta shows an increase in transfer rate of about 67 times from the middle of the third tenth of gestation to the maximum observed just before term. The observed change in the transfer rate is least spectacular in the goat, where it increases about five times during approximately the last half of gestation.

With the exception of the sow, all the placentas also have in common a peak or maximum transfer rate per unit weight shortly before term with a sharp drop in transfer rate as term is approached.

These findings immediately recall one of the questions asked in the introduction to this paper: What are the underlying causes for the observed increase in transfer rate per gram of placenta? A satisfactory answer to this question must involve quantitative knowledge of possible changes in such factors as size of placental capillary beds, rate of placental capillary blood flow, surface area across which exchange occurs, etc. All of these factors are unsatisfactorily understood. An important contribution has been made by numerous studies of Barcroft and his collaborators.[17-19]

Of clearer meaning at the moment are those morphologic changes found to occur as the placenta ages. A correlation can be made between changes in the placental structure and changes in the rate of transfer at different periods of gestation, but these are necessarily crude because of lack of quantitative measurements of tissue and cell relations. However, the general picture is clear and consistent. In the sow, there is a progressive diminution in the heights of chorionic and uterine epithelia.[16] In the goat, chorionic villi are covered with an inner cellular and an outer syncytial layer; in the later stages of pregnancy, the inner cellular layer thins and the syncytial layer becomes discontinuous. The cat, like the goat, has an inner cellular and an outer syncytial layer, and in this case aging of the placenta is accompanied by reduction in height and in places disappearance of the cellular layer. The rat, guinea pig, and rabbit, in the earlier part of the gestation period, have chorionic villi covered with a single layer. In later pregnancy, this layer thins and disappears to such a large extent that Mossman[20] has suggested the term "hemo-endothelial" for the placenta at this period. The fall in transfer rate near term is in all likelihood due to senile changes in the placenta, such as thrombosis of the maternal vessels with infarction, etc.

Fig. 2 presents the changes in rate of transfer of sodium across a unit weight of the rabbit's placenta as gestation proceeds. The figure also gives in schematic form those changes in the chorionic plasmodium or syncytium which have been described by Mossman[20] at various periods of gestation. The syncytium is complete at the eighteenth day, at the twenty-fifth day it is discontinuous, and it has practically disappeared at the thirtieth day. The transfer rate of Na across the placenta increases as these changes occur. The figure consequently presents the sort of correlation which can be made between known morphologic changes and the observed changes in function.

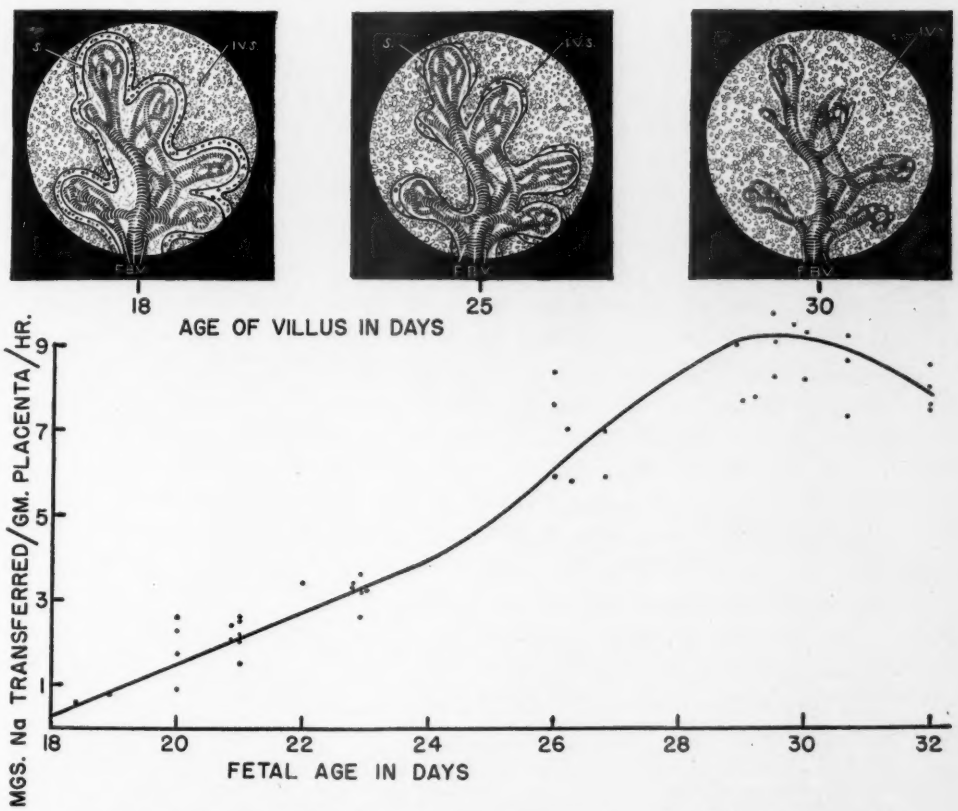

Fig. 2.—Changes in rate of transfer of sodium across a unit weight of the rabbit's placenta at different periods of gestation. The diagrams of the villi indicate the type of morphologic change which can be correlated with the functional change. *F.B.V.*, Fetal blood vessels; *I.V.S.*, intervillous space; *S.*, syncitium.

If this correlation be valid, an inspection of Fig. 1 indicates those intervals during which the maximum morphologic and physiologic changes in the placenta would be expected to take place. For example, in the case of the rat we would anticipate that more striking changes would occur between the eighteenth and twenty-second day than during those preceding. This is the period during which the transfer rate increases most rapidly.

2. *Correlation of Transfer Rate and Morphologic Type of Placenta.*—Grosser[21] has classified all placentas into four groups. This grouping depends upon the number of tissue layers separating the maternal and fetal circulations, as is evident from Table I, which has been taken from

TABLE I. CELLULAR LAYERS BETWEEN MATERNAL AND FETAL CIRCULATION. GROSSER'S CLASSIFICATION OF PLACENTAS

TYPE OF PLACENTA	MATERNAL			FETAL			EXAMPLES
	ENDOTHELIUM	CONNECTIVE TISSUE	EPITHELIUM	EPITHELIUM	CONNECTIVE TISSUE	ENDOTHELIUM	
Epitheliochorial	+	+	+	+	+	+	Sow
Syndesmochorial	+	+	−	+	+	+	Goat, sheep, cow
Endotheliochorial	+	−	−	+	+	+	Cat
Hemochorial	−	−	−	+	+	+	Guinea pig, rat, rabbit, man

Grosser. One of our purposes has been to study the variations in transfer rate which occur among these four types of placentas. It is apparent that a measure of the variation among placentas of the same group must be obtained in order to appraise properly differences in the behavior of placentas belonging to different morphologic groups. For this reason we have chosen to study one member of each of three groups and three members of the fourth group. The sow has been taken because it belongs to the epitheliochorial group; the goat, because it is syndesmochorial; the cat, because it is endotheliochorial; and the rat, rabbit, and guinea pig have been chosen as representatives of the hemochorial group. We have compared the transfer rates across these different placentas at corresponding parts of the total gestation period.

Fig. 3 presents schematically the type of tissue layers placed between maternal and fetal circulations in Grosser's four groups. Above the diagrams of the placentas, there is indicated graphically the amount of sodium transferred per gram of placenta per hour midway between the eighth and ninth tenths of gestation. Two important conclusions are evident from the data of the figure. The first is that there is little variation in transfer rate among the members of a single group. The maximum variation is between the rat and guinea pig, the former having a transfer rate approximately 40 per cent greater than the latter. This close correspondence holds as well for earlier and later stages of pregnancy.[13, 15] The second conclusion is that the greater the number of tissue layers placed between maternal and fetal circulations, the lower the unit transfer rate. Thus, the unit transfer rate of the rat's placenta with three tissue layers is 320 times that of the sow with six layers. It is also to be noted that the difference between the goat, a representative

of the syndesmochorial group, and the cat, of the endotheliochorial group, is relatively slight.

3. *Correlation Between Relative Growth Rate of Fetus and Rate of Transfer of Sodium to Fetus.*—Does the fetus receive a constant supply of sodium from the mother during the gestation period and incorporate with growth the amount which is needed while the remainder is returned to the maternal circulation? Or, does the supply of sodium vary during the gestation period according to the rate of fetal growth? The answer to these questions can be obtained by comparing the supply of sodium to a gram of fetus per unit time with the rate at which that gram of fetus reproduces itself. The first of these two quantities is found by

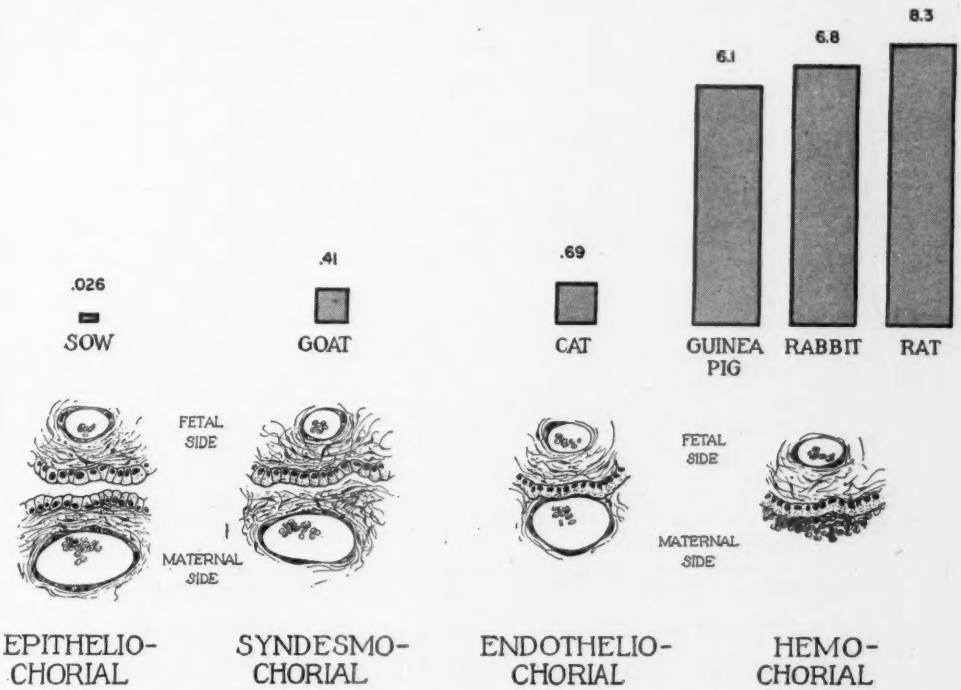

Fig. 3.—Variation of transfer rate per unit weight of placenta with the morphologic type of placenta. The numerical values give the mg. of Na transferred across a unit weight of placenta per hour as observed in each instance at the middle of the ninth tenth of pregnancy. The relative magnitudes of the transfer rates are indicated by the relative areas of the dotted rectangles. The diagrams indicate the number and kind of tissue layers interposed between maternal and fetal circulations in each of Grosser's four groups.

simply dividing the total sodium transferred to the fetus per hour by the fetal weight. The second quantity is the relative growth rate of the fetus and is obtained in a manner previously given[11] from the data relating fetal weight to gestation age. If the placenta is nicely adapted to the needs of the fetus, one would expect a large amount of sodium to be transferred per gram fetus when the relative growth rate is high, since sodium is an integral part of each unit mass of tissue, and a lower transfer rate per gram fetus when the relative growth rate is low.

Fig. 4 gives the relative growth rate and the transfer rate of Na per gram fetus at progressive fetal weights for the cat. It is evident that the two curves are similar; when the fetus is small and a unit weight of its tissue is reproducing itself rapidly, the transfer rate of Na to a unit weight of fetus is high, and as the fetus grows older and its relative growth rate drops, the supply of sodium per unit weight of fetus is commensurately low. This finding in the cat is typical of that observed in the other animals which have been studied.[11-16]

These results can be expressed in another way. As has been said, the curves of relative growth rate and rate of supply of sodium are similar. If this be strictly true, it follows that the rate of supply of sodium to a unit weight of fetus times a constant quantity should be equal to the relative growth rate at any fetal weight or fetal age, or K = relative growth rate ÷ transfer Na per gram fetus per hour. The precision with

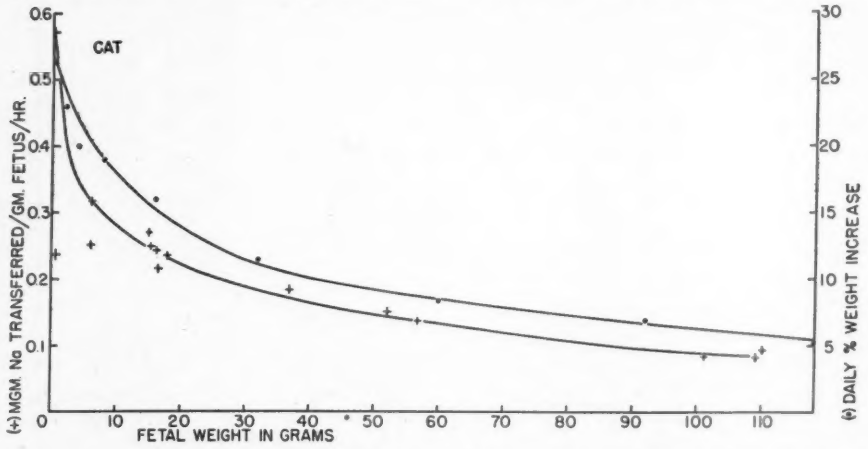

Fig. 4.—Comparison of curve of daily percentage weight increase and curve of transfer rate of sodium per gram fetus for the cat during the gestation period.

which this concept fits the observations will be evident from the variation in K at various parts of gestation. The value for K for the several animals and at different periods of pregnancy is given in Table II. It is apparent that the variation in K for a particular animal is remarkably small.

These findings suggest the hypothesis that the fundamental principle underlying placental function is that the rate at which substances are transferred to a unit weight of fetus shall parallel the relative growth rate of the fetus.

We have been further interested to inquire whether wide differences in the relative growth rates of the fetuses of different animals can be correlated with differences in the rate at which sodium is supplied to a unit weight of fetus. Thus, it can be seen in Table II in the middle of the seventh tenth of gestation that the rabbit is reproducing its weight at the rate of 25 per cent daily, whereas the goat is reproducing its

weight at a rate of only 2.2 per cent daily. Hence, the rabbit is growing about 11 times as rapidly as the goat. Is there a corresponding difference in the rates of supply of Na per unit weight of fetuses? Table II also shows that at this time the rabbit fetus is receiving about 13 times as much Na per unit weight as the fetus of the goat.

A clear concept of this relationship among the relative growth rates of the several kinds of fetuses and their corresponding rates of supply of Na can be obtained from comparing K of Table II from animal to

TABLE II. RELATIONSHIP BETWEEN RATE OF SUPPLY OF SODIUM PER GRAM FETUS (Na_F) AND RELATIVE GROWTH RATE OF FETUS (RGR). THE CONSTANT K IS CALCULATED FROM THE RELATIONSHIP: $K = \frac{RGR.}{Na_F}$

ANIMAL	GESTATION PERIOD IN TENTHS OF TOTAL											
	0.6-0.7			0.7-0.8			0.8-0.9			0.9-1.0		
	RGR	Na_F	K	RGR	Na_F	K	RGR	Na_F	K	RGR	Na_F	K
Goat	2.9	0.089	33	2.2	0.069	32	2.0	0.055	54	2.0	0.05	40
Cat	15	0.27	64	10	0.17	61	7.5	0.13	57	6.0	0.13	46
Guinea pig	12	0.46	26	10	0.39	25	8.0	0.33	24	8.0	0.28	28
Rat	62	1.0	60	52	0.75	60	47	0.79	60	38	0.63	60
Rabbit				25	0.92	27	19	0.79	24	27	0.93	30
Sow	5.8	0.0079	730	4.4	0.0062	710	3.3	0.0056	580	3.0	0.0050	580

animal. The value of K is of the same magnitude throughout with the unexplained exception of the sow. The maximum variation occurs between the cat and rabbit, the value of K in the cat being about twice that in the rabbit. It consequently becomes possible, knowing the value of K for a single fetus (guinea pig or rat, or rabbit, or goat, or cat), to estimate with a fair degree of accuracy the rate of transfer of sodium to any other fetus (excepting the sow) if the data, which are at hand, on the growth of that fetus are used.

A fundamental question that must be answered before placental physiology is completely understood was mentioned in the introduction. Does the placenta behave like an inert membrane between the maternal and fetal circulations, or does it contribute energy in the transfer of material from mother to fetus, thereby becoming a secretory organ? Before this problem can be solved, it is probable that the transfer rate of many physiologic substances across the placenta will have to be investigated not only from the mother to the fetus, but also in the reverse direction, from the fetus to the mother. The results of the present series of studies do not provide evidence either for or against secretion.

SUMMARY

The transfer of sodium across the placentas of six different animals at progressive stages of the gestation period has been studied. The rate of transfer of sodium per gram of placenta increases in each animal as gestation proceeds until just before term, at which time there is a sharp decrease. The variation in rate of transfer across the placentas has been correlated with morphologic changes in the placenta.

The animals have been chosen to give at least one representative of each of Grosser's morphologic types of placentas. The rates of transfer of sodium across unit weights of these four types of placentas have been found to depend upon the morphologic structure of the placenta: the smaller the number of tissue layers placed between maternal and fetal circulations, the greater the rate of transfer across a unit weight of the placenta.

A correlation was found to exist between the supply of sodium transferred to a unit weight of fetus and the rate at which that unit weight of fetus was growing. This constant observation in all of the animals studied leads us to propose the hypothesis that the underlying principle of placental function is that the rate at which a physiologic substance is transferred to the fetus shall parallel the relative growth rate of the fetus.

We are grateful to the staff of the Department of Terrestrial Magnetism, Carnegie Institution of Washington, for their generous help and advice. We are much indebted to Dr. Dean B. Cowie of the National Cancer Institute and to Dr. B. R. Curtis, Jefferson Physics Laboratory, Harvard University, for preparing the radioactive sodium with the Carnegie generator and the Harvard cyclotron.

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DIFFUSE LUTEINIZATION OF THE OVARIES ASSOCIATED WITH THE MASCULINIZATION SYNDROME

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CONSPICUOUS masculinizing changes in the human female have been associated with a variety of lesions of the endocrine glands. Certain among these appear to be unequivocally responsible for the clinical syndrome; namely, hyperplasia, adenoma or carcinoma of the adrenal cortex, and arrhenoblastoma or adrenal rest tumors of the ovary. The primary importance of other lesions including basophile cell changes in the pituitary (Cushing's syndrome), or thymic neoplasms has been seriously questioned in recent years.[12] It has been shown in a large number of cases of so-called pituitary basophilism in which autopsy reports were available, that either hyperplasia or adenoma of the adrenal cortex was present in addition to the hypophyseal lesion.[3] Furthermore, in 2 to 3 per cent of routine post-mortem examinations, small basophilic adenomas of the anterior pituitary gland have been uncovered purely incidentally, without evidence of virilism.[13] Similarly, in those cases attributed to thymic tumors, adrenal cortical hyperplasia was also found, while the pituitary gland was reported as negative.[17] Thus, in a consideration of the syndrome of masculinization, exclusive of those cases associated with defeminizing tumors of the ovary, it appears that the common, morphologic denominator responsible for the symptom complex may well be either hyperplasia or neoplasia of the adrenal cortex.

In this report we are primarily concerned with the status of the ovaries in such cases. Clinical descriptions of the syndrome indicate that the ovaries are generally small or normal in size, and that evidence of genital regression is usually present, associated with oligomenorrhea or amenorrhea. In this laboratory, we have had the opportunity of studying the post-mortem material of 10 cases of virilism; 7 with cortical adenoma and 3 with carcinoma of the adrenal gland. Of these, all had experienced amenorrhea of three to seventeen months' duration. Examination of the ovaries showed them to be small or normal in size, with little evidence of follicular activity. Recent corpora lutea were not present, corpora albicantia were relatively conspicuous, and the small cystic follicles occasionally encountered were atretic. A survey of the literature in which full autopsies were reported substantiated these findings.[2-4, 6, 10, 11, 15, 18, 19] The gonads were generally described as small, atrophic, fibrotic, senile, or sclerotic, containing some atretic follicles

and old corpora albicantia. In only one instance, published by Bergstrand in 1934, did the ovarian changes approach those described in this report.[1]

It would seem from the above findings that a palpable enlargement of the ovaries is not to be expected in patients manifesting adrenogenitalism. Indeed, in those cases of virilism in which an ovarian enlargement or tumor is found on pelvic examination, the suspicion of a masculinizing ovarian tumor must be entertained. It is the purpose of this report to demonstrate that the latter assumption may be false, for in the two cases described below, a typical clinical picture of masculinization was found associated with enlarged ovaries, due, not to an arrhenoblastoma or adrenal rest tumor, but to diffuse lutein changes particularly involving the theca interna cells.

CASE 1.*—M. G., a 32-year-old negress, was admitted to the City Hospital of New York in 1934. She had been married for two years and had never been gravid. The menses had begun at 13 years, and were always irregular, with amenorrheic periods up to four months. The menstrual flow, though at times scanty, occasionally continued for one to four weeks. Obesity had been present since the menarche. Progressive hirsuties of the face and chest continued from the age of 16, necessitating shaving at regular intervals. Metrorrhagia had been present for eight months before admission. On pelvic examination both ovaries were found to be enlarged to about twice normal size. A preliminary dilatation and curettage revealed "a small amount of tissue." A laparotomy was then done and both ovaries removed. The ovaries were uniformly enlarged. On section there were several cystic follicles, while the solid portions of the ovary had a distinct yellowish hue. A portion of the ovaries was made available to us for microscopic study.

Three years later in 1937 the patient was admitted to the Mount Sinai Hospital for further investigation. The obesity and hirsuties were still present (Fig. 1). She was amenorrheic and complained of frequent hot flushes. Examination revealed the following: There was diffuse trunk and girdle obesity, while the extremities were relatively normal. The face was round and obese, and the neck short and thick. She weighed 188 pounds and was 5 feet, 3 inches tall. There was a conspicuous hypertrichosis of the face and chest, with a tendency to a male type of escutcheon. The clitoris was not enlarged. Blood pressure was 140/80; urinalysis, negative; basal metabolism, +2 per cent; the blood count showed no abnormalities; blood Wassermann reaction, 1+; sedimentation time, normal. The pupils were unequal. The visual fields were normal. X-ray of the sella turcica revealed no abnormalities. Intravenous pyelogram was negative, without evidence of distortion of the upper calyces of the renal pelves. Perirenal insufflation outlined the right adrenal gland, but showed no abnormalities in its contour. On bimanual examination the uterus was found to be small and the pelvis clear.

Our interest in this patient had been stimulated originally by the unusual ovarian findings. Despite the absence of a demonstrable lesion of the anterior hypophysis or adrenal gland, the clinical picture was

*We are indebted to Dr. Maurice Rashbaum and Dr. James R. Lisa of the City Hospital for the opportunity to study this case.

classified as one of adrenogenitalism, unaffected by previous bilateral oophorectomy. Further follow-up was not obtainable.

Histology of the Ovaries.—The ovarian parenchyma presents a most striking histologic change. Scattered throughout the cortex and medulla are numerous groups of large, foamy cells. These are distributed diffusely throughout the ovary in irregular strands or accumulations of varying size (Fig. 2). They resemble well-developed, luteinized theca cells. They are large, round or oval, with light staining, finely vacuolated cytoplasm, round vesicular nucleus and distinct nucleolus. The picture brings to mind the so-called "interstitial gland" sometimes

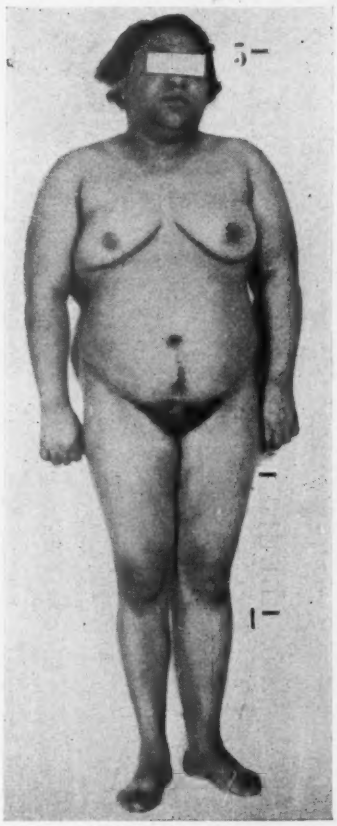

Fig. 1.—Case 1. Masculinizing changes associated with enlarged, luteinized ovaries. Note girdle, trunk, and facial obesity. The patient shaved regularly. Oligomenorrhea and metrorrhagia had been present since the menarche.

seen in ovaries of lower animals, or the diffuse, parenchymal luteinization encountered in mice following x-ray.[8] The presence of these cells adjacent to old corpora albicantia suggests at first glance, a possible origin from dormant theca cells about the corpora albicantia. The latter, however, are so numerous that the contiguity may be merely coincidental. Furthermore, the luteinized cells appear elsewhere in areas free of follicle structures. The ovarian parenchyma suggests increased proliferation, not only because of the increased thickness of the ovary, but also because the parenchyma shows distinct variations in cellularity, staining reaction, and size and shape of the cells. The theca zone about

atretic follicles is increased in thickness. Even in atretic follicles where the granulosa is reduced to a single layer of flattened cells, the theca cells show excessive proliferation and luteinization (Fig. 3).

CASE 2.—B. G. (Admission No. 405620, Path. No. 58999), aged 27 years, married five years, gravida 0. Regular menstrual periods had occurred from the menarche at 13 years until the age of 22 years. In

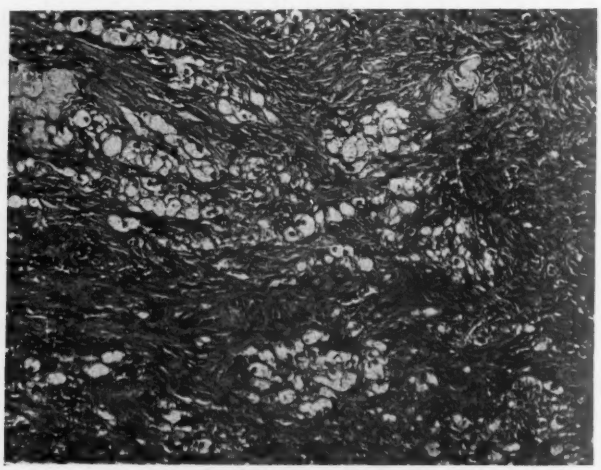

Fig. 2.—Case 1. Groups of enlarged, luteinized cells, irregularly scattered throughout the ovarian parenchyma.

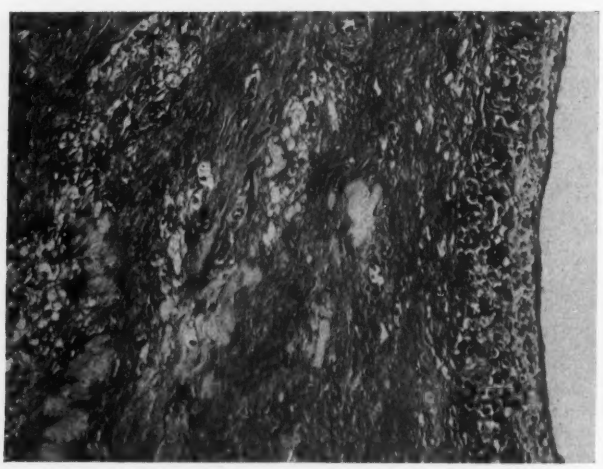

Fig. 3.—Case 1. Wall of atretic follicle showing flattened, granulosa layer with proliferation and luteinization of the theca interna. Note lutein cells in the ovarian cortex.

the ensuing five years, however, the patient was amenorrheic except for three monthly periods of bleeding one year before admission. Despite the absence of menstruation, molimina consisting of pelvic pressure and general fatigue were experienced at monthly intervals. During this time the voice changed from a definite soprano to baritone. Increasing

growth of hair about the face and trunk was noted, necessitating shaving on alternate days. There was a gain of 40 pounds in weight. In addition, for three months before admission the patient complained of frontal headaches, intermittent attacks of epigastric pain, dyspnea, nausea, and occasional vomiting.

On examination the obesity was confined mainly to the head and trunk, sparing the upper and lower extremities. The face was round and full. There was marked hirsuties of the face, chest, back, abdomen, and extremities (Fig. 4). The escutcheon was of the male type. The clitoris was enlarged to four times normal size. On pelvic examination, the uterus was normal in size and retroverted. In the cul-de-sac and to the left a fullness was felt, suggestive of ovarian enlargement. Blood pressure was 130/80 to 160/100; hemoglobin, 106 per cent; red blood

Fig. 4.—Case 2. Typical picture of virilism including obesity and marked hypertrichosis.

count, 5,000,000; white blood count 7,550 with normal differential count; basal metabolism, +11 per cent and +20 per cent; total proteins, 7.8 Gm. per cent; albumin, 5.7 Gm. per cent; globulin, 2.1 Gm. per cent; blood sugar, 90 mg. per cent. Blood Wassermann reaction was negative. Rehfuss test, the electrocardiogram, and visual fields were normal. Gastrointestinal series, chest x-ray, x-ray of elbows and wrists, intravenous pyelogram, x-ray of the sella turcica, and bilateral perirenal insufflation tests were all found to be negative. Because of the pelvic findings and the lack of a demonstrable lesion of the pituitary or adrenal glands, laparotomy was performed. The uterus was found to be slightly enlarged and retroverted. The left ovary was cystic, enlarged, and adherent to the lateral pelvic wall. On the right side, the appendix had

become adherent to the ovary and the latter bound down to the pelvic floor. Bilateral salpingo-oophorectomy and appendectomy were done. Convalescence was uneventful. A short time later the patient left the city, so that an adequate follow-up could not be obtained.

Gross Examination.—The right ovary measured 5 by 3.5 by 3.5 cm. in the unfixed state. On cut section numerous follicle cysts, varying from 2 to 7 mm. in diameter, rimmed the periphery (Fig. 5). No mature or recent corpus luteum was evident. The medullary portion of the

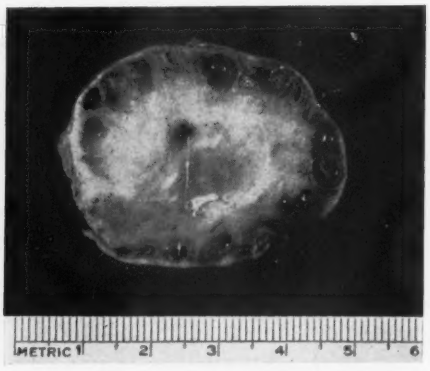

Fig. 5.—Case 2. Cross section of right ovary showing several cystic follicles. The medullary portion was of yellowish hue.

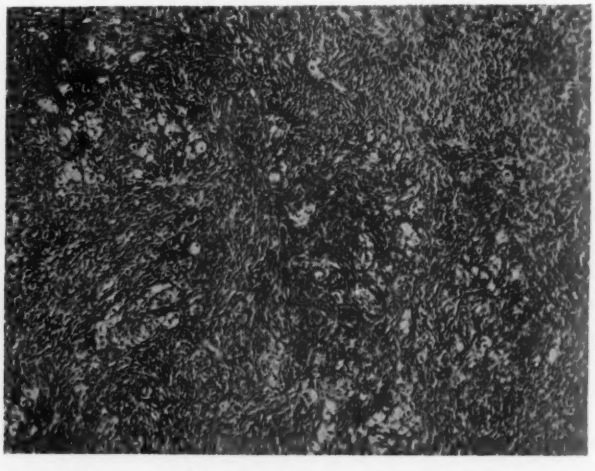

Fig. 6.—Case 2. Small groups of luteinized cells distributed irregularly throughout the parenchyma of the ovary.

ovary appeared hyperplastic and was gray yellow in color, with scattered orange yellow flecks. The left ovary was of similar size and color. Cystic follicles were not as abundant. At one pole a portion of the collapsed wall of a hemorrhagic cyst was evident.

Microscopic Examination.—Within the ovarian cortex, primordial and maturing follicles were distributed in normal numbers. The majority of the atretic follicles presented an unusual degree of perifollicular proliferation of the theca interna zone, with evidence of increased luteinizations of the theca cells (Fig. 7). Such stimulation was seen at times

about follicle cysts in which the granulosa lining had been reduced to a single, flattened layer of cells (Fig. 8). In other atretic follicle cysts, the granulosa cell lining might show increased cellular activity only in one portion of its circumference, while the theca interna cells showed more uniform hyperplasia. Scattered throughout the ovary in both

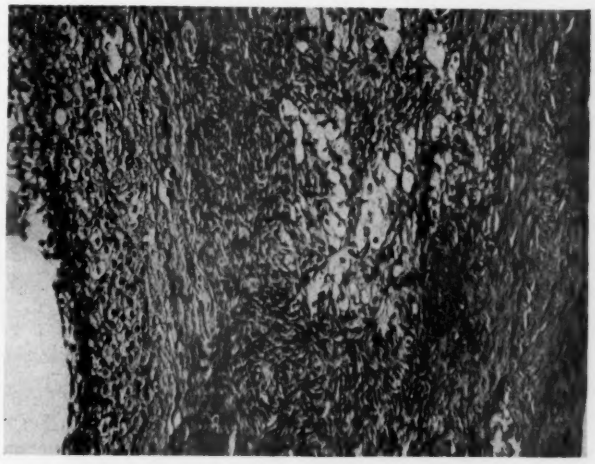

Fig. 7.—Case 2. Perifollicular, theca growth and luteinization. Note lutein cells in the cortex.

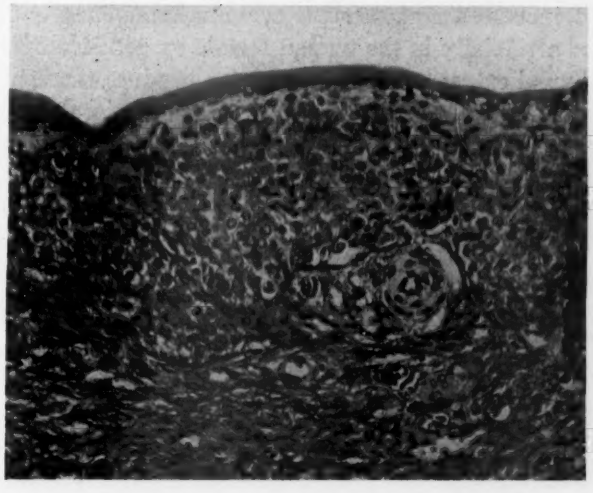

Fig. 8.—Case 2. Atretic follicle with flattened granulosa cells and unusually conspicuous stimulation of the theca interna.

cortex and medulla (Fig. 6) were irregular groups of large, vacuolated, luteinized cells, similar to those described in Case 1, but to a much lesser degree. Although many corpora albicantia were present, a recent corpus luteum could not be found.

DISCUSSION

In two cases of masculinization, luteinization of the ovaries has been found. It is apparent that this must be an unusual or even rare occur-

rence in the arrhenomimetic syndrome. It appears unlikely that the ovarian changes described are directly responsible for the clinical picture. In Case 1 there was no regression of the virilism following bilateral oophorectomy. Although a lesion of the pituitary or adrenal glands was not demonstrated clinically in the 2 reported cases, their presence or the possibility of functional alterations cannot be ruled out. Pregnanediol studies were not performed in our cases. They may be of diagnostic value in some types of hirsuties, since an excretion of pregnanediol in appreciable amounts has been found in cases of carcinoma or hyperplasia of the adrenal cortex associated with virilism.[20] Fortunately, there is available a report by Bergstrand in which the ovarian findings paralleled those in Case 2, and in which a complete autopsy was secured.[1] His patient was a woman, aged 42 years, whose clinical course was entirely similar to those described here. The ovaries were enlarged and yellowish. There were many atretic follicles with perifollicular zones of luteinized theca cells. At autopsy a large basophilic adenoma of the pituitary gland and diffuse hyperplasia of both adrenal glands were found. The weight of evidence, therefore, would suggest that the ovarian alterations are secondary and not directly responsible for the masculinization syndrome.

The ovarian histologic changes described in this communication are suggestive of increased gonadotropic stimulation. They are not unlike those induced artificially in the human female by gonadotropins, particularly hypophyseal extracts.[9] The latter may produce theca proliferation and luteinization, perifollicular hemorrhage, and stimulation of granulosa and theca cells in follicles showing various stages of atresia, without, however, any evidence of increased follicle maturation, ovulation or corpus luteum formation. The excessive luteinization of theca elements in our cases, though not exactly similar may also be compared with the conspicuous theca proliferation and luteinization seen in cases of hydatidiform mole or chorionepithelioma, in which the gonadotropins are greatly increased.

It is interesting to note that similar histologic ovarian changes have also been reported in intact, suckling, female rats, following the administration of gonadotropins, and that these effects were accompanied by evidences of masculinization.[15, 16] If injections of chorionic or equine gonadotropins are given from the sixth to the twenty-sixth day of life, follicle maturation and corpus luteum formation do not occur at that time; instead, ovarian enlargement is found to be due to perifollicular proliferation and luteinization of the theca cells, suggesting the appearance of the so-called "interstitial gland." These changes are accompanied by such masculinizing characteristics as hypertrophy of the clitoris and prepuce. Because the androgenic effects do not occur in ovariectomized animals, it was assumed that the altered ovaries were responsible for the production of an androgenic substance. However,

this inference is not entirely warranted, since the function of the adrenals may also have been affected.

SUMMARY

The syndrome of masculinization in the female, attributed to pituitary basophilism or adrenal cortical lesions, usually includes regressive changes in the ovaries. At times, however, as evidenced by the two cases described in this report, there may be bilateral ovarian enlargement, due to excessive perifollicular proliferation and luteinization of the theca cells and diffusely scattered luteinized cells within the ovarian parenchyma.

The ovarian effects are suggestive of increased gonadotropic stimulation and are probably secondary. It does not appear that they are responsible for the production of the masculinization syndrome.

In the clinical investigation of virilism the presence of an ovarian enlargement has been and should be regarded as suspicious evidence of a possible arrhenoblastoma or adrenal rest neoplasm of the ovary. In view of this report, a third possibility exists, namely, enlargement of the ovary due to diffuse luteinization. It may be possible to decide, at operation, by incision of the ovaries, whether or not tumor is present. If, in young patients, tumor can unequivocally be ruled out by this device, one or both ovaries may be left in situ.

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THE CYTOLOGIC RELATIONSHIP OF THE WALTHARD CELL REST TO THE BRENNER TUMOR OF THE OVARY AND TO THE PSEUDOMUCINOUS CYSTADENOMA

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MOST authorities agree that Brenner tumors of the ovary probably have as their anlagen the cell rests described by Walthard in 1903. In addition, the occasional finding of Brenner tumors in the walls of pseudomucinous cystadenomas of the ovary, and the more frequent finding of pseudomucinous epithelium in Brenner tumors and Walthard rests, have been cited as indications that at least a portion of the pseudomucinous cystadenomas may have their origin in Brenner tumors. If these inferences are true, one might expect to find certain cytologic as well as architectural features common to all three structures. It is the purpose of this communication, first, to describe more minutely the cells making up the Walthard rests, the Brenner nests, and the pseudomucinous cystadenomas of the ovary, and, second, to indicate certain points of similarity. Upon the basis of these descriptions it seems possible to offer further indication of their common origin, and also to suggest a third criterion for the diagnosis of the Brenner tumor.

A detailed review of the literature concerning these structures seems unnecessary, since it is considered in all recent textbooks and articles dealing with the subject.

The *Walthard rest* is a small collection of cells which may be found in the cortex or hilus of the ovary, or beneath the serosa or within the mesosalpinx of the Fallopian tube. The rests are of two types, the solid and the cystic. In the cystic type the central portion of the rest is occupied by a clear space which is said to contain mucin or pseudomucin, colloid, or mixed material. The cystic cavity is ordinarily lined by from one to ten or more layers of cells. There appears to be no accurate estimate of the frequency of these rests except that of Muller, who found them in 12 per cent of 251 adnexa examined. The origin of the Walthard rests is obscure. They are stated variously to arise from the coelomic epithelium of the developing embryo, from an inflammatory reaction of the peritoneum, from the germinal epithelium and from numerous other structures. The first named is probably most widely accepted.

The *Brenner tumor* is one of the group of rare ovarian tumors, less than 150 of them having been reported. They may occur in women of

all ages, but are said to be more common in middle or late middle age. They may vary in size from a few millimeters in diameter to more than seven kilograms in weight. Their diagnosis is based wholly upon microscopic findings, since they have no gross or clinical characteristics which are peculiar to these tumors alone. Histologically, two criteria have been mentioned as essential for their diagnosis. These are, first, the presence of small characteristic cell nests which are, second, surrounded by a zone of fibrous tissue. The latter may be sufficiently extensive to give the gross impression of a fibroma. Two types of Brenner tumor have been described, though intermediate and mixed varieties are not uncommon. The first of these is the solid type, in which the cell nests are composed of rather closely packed cells. The second is the cystic type, in which the central portions of the nests are occupied by clear spaces. These spaces may be empty, or they may be filled by large nondescript cells, or by pseudomucin, or mixed material.

The *pseudomucinous cystadenoma* is sufficiently well known that its characteristics need not be mentioned here.

The reason why the Walthard rests were first incriminated as precursors of the Brenner tumor is not entirely clear. Perhaps it is because the Brenner tumors bear a very close qualitative resemblance to the rests; the major anatomic difference appears to be quantitative. The chief objection to this theory of the evolution of the Brenner tumor is that the tumors have never been observed in the tube, where the rests are commonest. The customary explanation of this discrepancy is that the tube is notorious for its indifference to tumor growth of all kinds despite the presence of tissues which in other sites may give rise to tumors of enormous size and variation. The fundamental reason for this indifference will probably be found only when the precise conditions necessary for tumor growth in any site are determined.

The observation has been made that in occasional instances the cystic Walthard rests may be lined in part by pseudomucinous epithelium, the latter merging imperceptibly with that of the heavier portion of the rest wall. This has also been observed in some of the cystic Brenner tumors and, in addition, true Brenner tumors have been reported in the walls of pseudomucinous cystadenomas. The latter finding is cited in support of the contention that in occasional instances, the cystadenomas may arise from previously existing Brenner tumors. This purported evolutionary relationship is indeed highly circumstantial, since it is impossible to establish it upon a sound experimental basis. Additional observations may strengthen or weaken this hypothesis, but will probably fall short of absolute proof. The material presented herewith adds weight to the belief that the Walthard rests, Brenner tumors, and pseudomucinous cystadenomas are fundamentally related to one another. Precisely what this relationship is cannot be stated.

MATERIALS AND METHODS

Tubes, Ovaries, and Cystadenomas.—This material consists of single microscopic sections of 350 consecutive normal Fallopian tubes and of 100 essentially normal ovaries, together with at least three slides each of 50 benign, uncomplicated pseudomucinous cystadenomas.

Brenner Tumors.—The Brenner tumor material available for study consists of 18 tumors. This is not a large number. It comprises, however, something more than one-tenth of the Brenner tumors which have been reported. Of these, 11 are among the slide collection of the Laboratory of Gynecological Pathology of the Johns Hopkins Hospital, and were studied with the kind permission of Dr. Emil Novak. Four tumors were made available through the kindness of Dr. W. C. Danforth of Northwestern University. The remaining three were observed in the pathologic laboratory of the Sloane Hospital for Women; they are the only Brenner tumors which have been observed here in the nine years since they were first clearly described and classified by Robert Meyer. During this time more than 10,000 obstetric and gynecologic cases have been studied. These three tumors have not been reported hitherto. The first tumor, observed in 1933, was of the solid type. The patient was a 38-year-old colored female, who complained of menorrhagia. At operation the associated pathology was found to consist of fibromyomas of the uterus, pelvic peritoneal adhesions, and chronic salpingitis. The ovaries were normal in appearance except for numerous filmy adhesions which enveloped them. The Brenner tumor was an incidental microscopic finding. The tumor is illustrated in Fig. 2. The second tumor, seen in April, 1940, was of the semisolid type. It is shown in Fig. 4. The patient was a 36-year-old colored female who complained of menorrhagia and metrorrhagia. At operation associated pathology was found to consist only of fibromyomas of the uterus. The adnexa were grossly normal. The Brenner tumor was an incidental microscopic finding. The third tumor, observed in October, 1940, was mixed, containing solid and cystic nests in approximately equal proportion. The patient was a 41-year-old white female who complained of menorrhagia. The associated pathology consisted of a placental polyp, myometritis, and chronic salpingitis. The adnexa were covered by filmy adhesions. The Brenner tumor was an incidental microscopic finding.

In the instances of the Fallopian tubes and ovaries, a careful examination was made for the presence of Walthard rests. The Brenner tumors, cystadenomas, and the entire series of Walthard rests were then studied with reference to cellular detail and, more precisely, to nuclear detail.

All of the routine slides are stained with hematoxylin and eosin. All of our own material was fixed by the Zenker's technique. In many instances blocks were recut so that special stains might be made.

RESULTS

In the *tube,* almost four times as many cystic rests were found as solid ones. In occasional instances the decision as to whether cystic or solid was difficult due to the fact that some were mixed, others intermediate. The rests occurred with approximately equal frequency beneath the serosa of the free edge of the tube, and within the mesosalpinx.

TABLE I. WALTHARD RESTS

	NUMBER OF ROUTINE SECTIONS EXAMINED	TOTAL WALTHARD RESTS FOUND		CYSTIC WALTHARD RESTS		SOLID WALTHARD RESTS		AVERAGE AGE OF PATIENTS
		NO.	% OF NO. EXAMINED	NO.	% OF TOTAL RESTS	NO.	% OF TOTAL RESTS	
Fallopian tube	350	56	16	43	77	13	23	41
Ovary	100	5	5	4	80	1	20	43

The average age of the patients is indicated. The oldest patient in this series of 56 cases was 53 years, the youngest 15. Six patients were negroes, the remainder white. The most common associated pathologic findings included fibromyomas of the uterus (29 cases), endometriosis (6 cases), and adenomyosis (3 cases). Five patients were sterilized by resection of the tubes; 3 of these were pregnant at the time of operation. At least 21 of the patients were parous, and at least 12 nulliparous.

When the solid tubal rests are examined with the very low power objective of the microscope (30× magnification), they give the impression of a nest of very closely packed basophilic cells. With a little higher magnification (90×), the cellular detail is still not evident, but one sees readily that the structure is surrounded by a zone of fibrous tissue of varying thickness. With the high dry objective (400×) or, preferably, with the oil immersion lens (900×), the details become apparent. The most striking feature of the cells is the nucleus, which is not simply round or ovoid, as it has been described, but in addition is seen to be marked or "tagged" in a specific manner. This marking consists of a tiny groove or fold which traverses the long axis of the nucleus in such a manner as to remind one of a coffee bean, or a kernel of puffed wheat. In many of the rests this characteristic marking is present in approximately 9 of 10 nuclei, being evident as a straight, bold line through the long axis, dividing the nucleus into two almost equal halves. As nearly as can be ascertained, this basic pattern is characteristic of one of the flat surfaces of a healthy, nondegenerate nucleus. In these instances the nuclear material is seen to be very finely granular and to contain, generally, one or two nucleoli. When two nucleoli are present, one usually appears upon either side of the dividing groove. In some cases the nucleoli take a pink stain. In rests such as these the outlines of the individual cells are generally not apparent, only a very fine reticulum appearing to lie between the nuclei.

Within the same rest numerous variations of the basic nuclear pattern may be seen. These appear to depend first upon the angle from which the cell is viewed, and second, upon the stage of development or regression which the rest has reached. Not infrequently the groove or

fold appears to be oblique, giving the impression that the marked surface of the nucleus is viewed from an angle. In other instances some of the nuclei may be shaped like coffee beans which are viewed toward one pole. Occasionally the nucleus is long and ovoid, as though viewed from the side.

The second type of variation, believed to be of a regressive nature, is seen occasionally in the solid rests, but far more commonly in the cystic or intermediate variety. The most striking alteration of this type occurs in the nuclei, with regard both to their distribution and morphology. At first glance it is readily evident that the individual nuclei are much farther apart than in the rests described above. The nuclei show no significant alteration in size, but may be extremely variable in shape and detail. A small proportion of the nuclei (at least one in ten) are

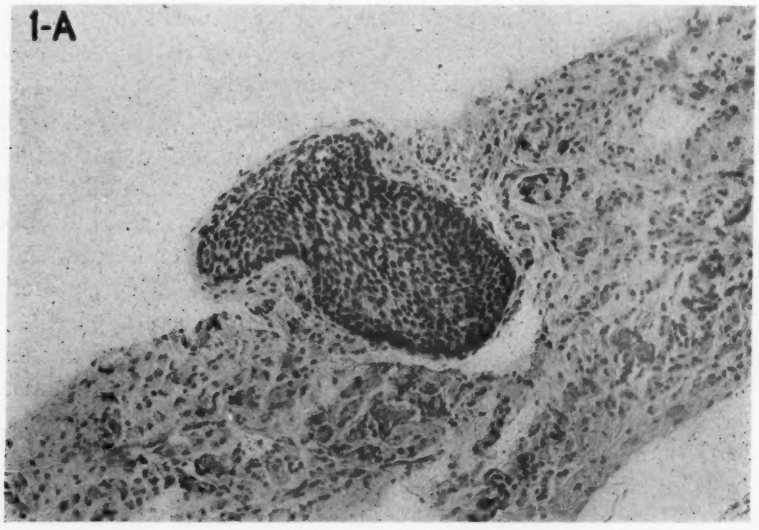

Fig. 1.-A.

Fig. 1.—*A*, Solid Walthard rest of tube (approximately 90×); *B*, oil immersion photomicrograph, same rest (approximately 900×); *C*, drawing of same field as *B*, to indicate detail which is not evident in *B*, since in the latter only occasional cells are in focus at the same time.

of the basic type. The remainder show various deviations. These are manifest especially as shortening, irregularity or complete absence of the median fold, loss of the granular quality of the nuclear material, absence or infrequency of nucleoli, and irregularity or wrinkling of the nuclear outline. In addition, the cell outlines in instances such as this are generally quite distinct, the cells now being evident as round, ovoid or polyhedral in shape, and of large size. The cytoplasm is clear and highly refractile, being seen only as a clear space which surrounds the nucleus.

Although nuclear deviations are more common in rests of the cystic or intermediate type, they may be seen occasionally in solid ones.

Furthermore, in many of the cystic rests, the great majority of the cells are of the basic type. Generally the more peripheral cells are typical, while the ones near the central cavity show one or more of the degenerative changes indicated above. In occasional cystic rests, the heavier

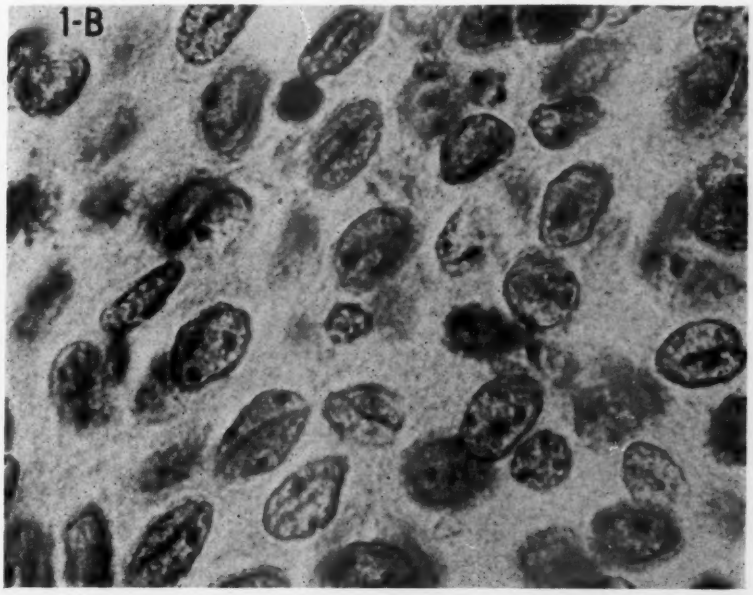

Fig. 1.-*B*.

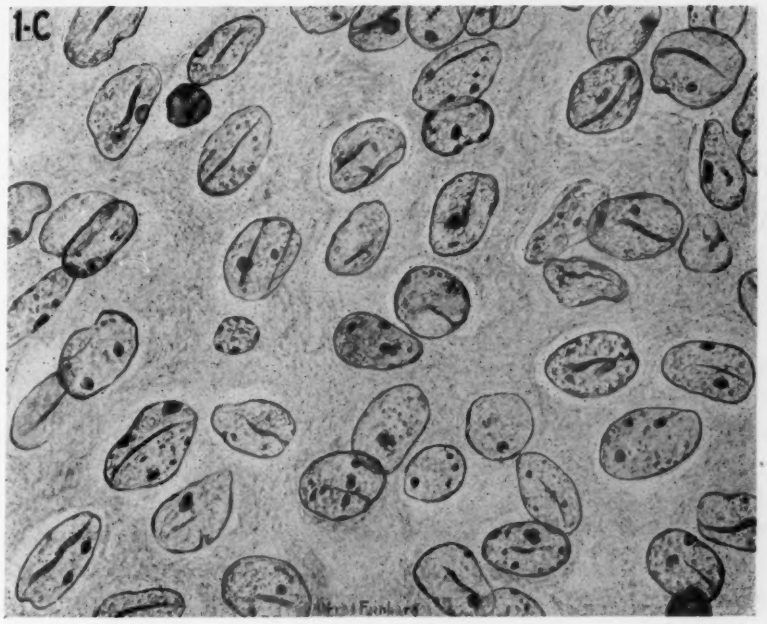

Fig. 1.-*C*.

portion of the cyst wall may be seen to fade gradually into a single layer of epithelium which is indistinguishable from that which is typical of the pseudomucinous cystadenoma. Others may be lined in part by a single layer of squamous epithelium which shows no resemblance to the basic cell type observed in the remainder of the rest.

In the ovary the incidence of Walthard rests was far less. This does not indicate necessarily that they occur here with less frequency, but rather suggests that our routine sections may not have been taken through a portion of the ovary which would include them. When seen, ovarion rests were found in the ovarian stroma a short distance below the germinal epithelium. It is of interest that the nuclear peculiarities of the rests distinguish them from tangentially sectioned ova. In two

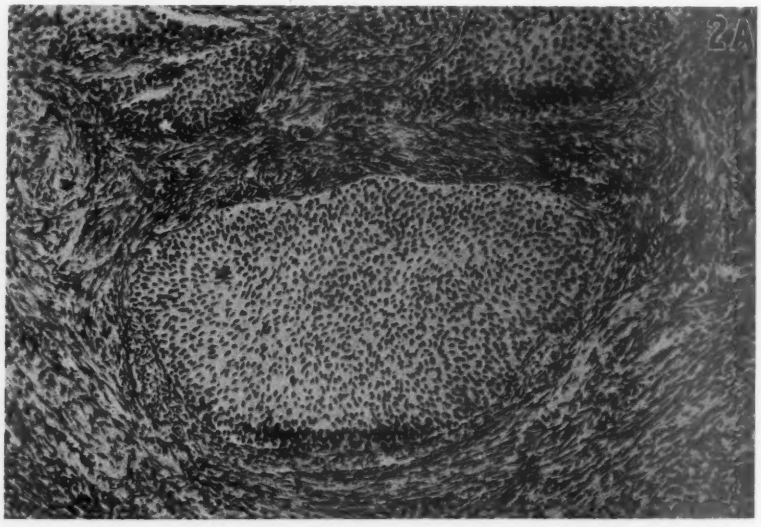

Fig. 2.-*A*.

Fig. 2.—*A*, Solid Brenner tumor (90×); *B*, oil immersion photomicrograph, same cell nest (900×); *C*, drawing of same field as in *B*. Fig. 1 was a rest selected to show similarity of rest to Brenner tumor, and to correspond in general to the solid tumor.

instances, tangential section of the germinal epithelium showed the latter to be made up of cells resembling the basic type previously described. These are not included in the five rests entered in Table I, since they do not conform to the definition of Walthard rests. The similarity of structure does suggest, however, that they are in some wise similar to the true rests discussed. Of the patients showing ovarian rests, 4 were white, 1 was a negro; 3 were parous, 2 nulliparous; none had reached the menopause. Associated pathologic findings included endometriosis (two cases) and fibromyomas of the uterus (three cases). One of the latter was complicated by chronic salpingitis.

Brenner Tumors.—The general architecture of the Brenner tumor has been outlined above. In all instances but one, in which faulty fixa-

tion had obscured the cellular structure of the entire tumor, the Brenner tumors examined were seen to be strikingly similar in cytologic detail to the Walthard rests which were described above. The nuclei contain the same fold or groove. The same nuclear variations are present, being accompanied by the other cytologic deviations mentioned previously.

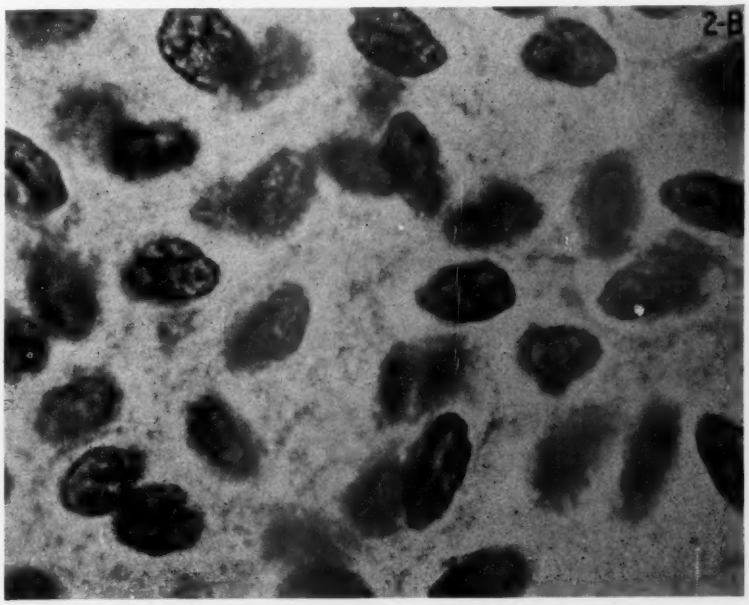

Fig. 2.-*B*.

Fig. 2.-*C*.

The incidence, distribution, and size of the nucleoli are similar. Only one primary difference has been observed between the cytologic aspects of the Walthard rests and the Brenner tumors: the nuclei may show slightly more variation in size. *In all of the Brenner tumors the basic nuclear type appears in sufficient frequency to be regarded as a funda-*

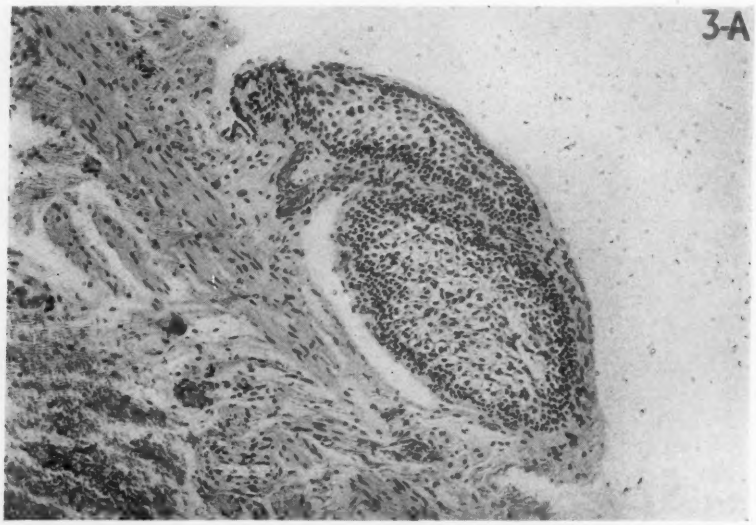

Fig. 3.-*A*.

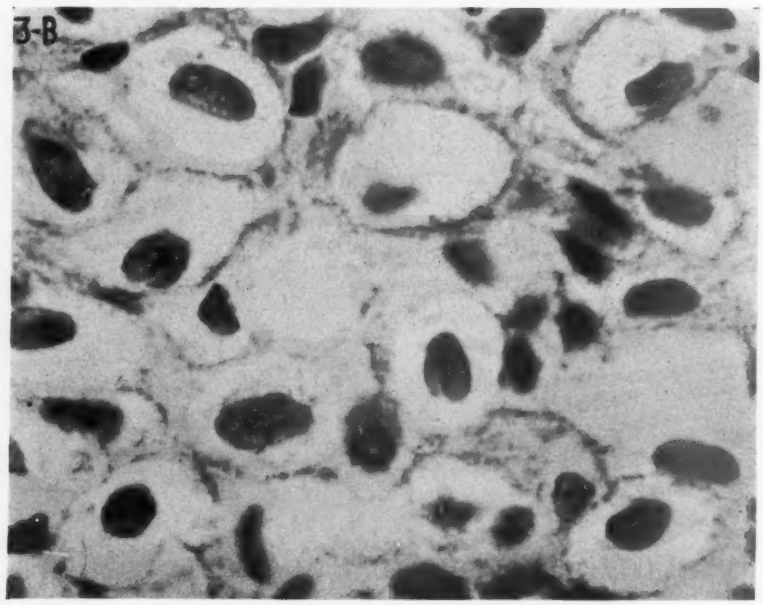

Fig. 3.-*B*.

Fig. 3.—*A*, Semisolid Walthard rest of tube (90×); *B*, oil immersion photomicrograph, same rest (900×).

mental characteristic. Figs. 1 to 4 illustrate the close cytologic similarity of the Brenner tumor to the Walthard rest.

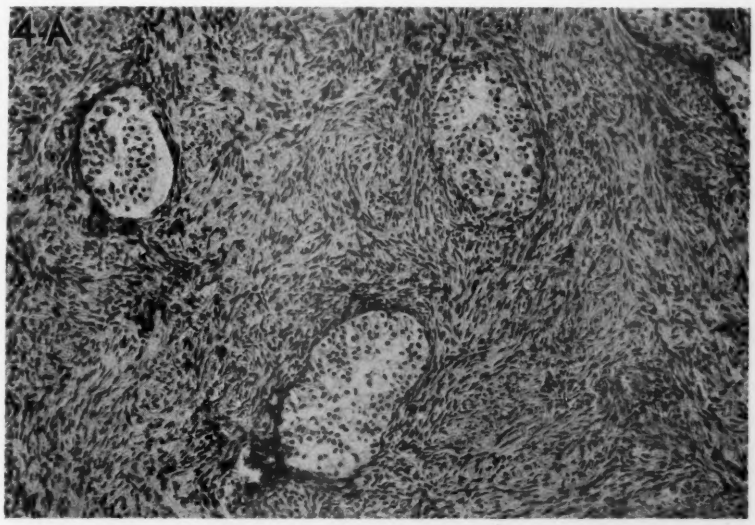

Fig. 4.—*A.*

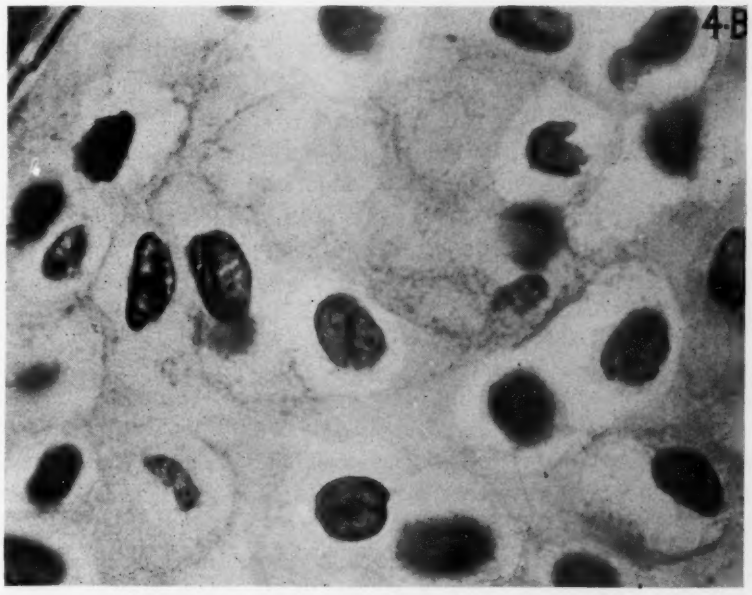

Fig. 4.—*B.*

Fig. 4.—*A*, Semisolid Brenner tumor (90×); *B*, oil immersion photomicrograph same nest (900×). (Compare with Fig. 3.)

Pseudomucinous Cystadenomas.—No Brenner tumors were found in careful examination of the pseudomucinous cystadenomas. It will be recalled that the characteristic cell of this tumor is of tall columnar type, with clear refractile cytoplasm, and deeply staining, small, often

crescent-shaped nuclei which are located close to the basement membrane. Most tumors, however, contain one or more areas where the epithelium is somewhat shorter, the nuclei ovoid in shape, and somewhat more lightly staining. Many of the cells in these areas approach a cuboidal, or even polyhedral shape. Novak states that cells such as this are of the immature type, and that they evidence active proliferative activity. *It is in this group of cells that one finds the only common cytologic link between this tumor and the Brenner.* In many of these immature cells the nuclei show a striking and rather precise similarity to those which have been termed the basic nuclear type. This similarity is especially evident where the epithelial layer has been cut tangentially, as here the nuclei may be seen in a relationship to one another which is like that noted in the other two situations. In occasional instances where the base of one of the cyst lobules is cut across, the cells appear to be embedded in a heavy zone of fibrous tissue and thus bear a strong resemblance to the Brenner cell nest and the Walthard cell rest.

Special stains have revealed no information which is not evident by the routine hematoxylin and eosin stains. Iron hematoxylin stains have in some instances accentuated the nuclear details, but add no new information. Stains for mucin and pseudomucin have been rather disappointing in the Walthard rests and Brenner tumors. In occasional instances the central portion of a cystic rest is seen to take a deep stain, but ordinarily the cyst contents have not withstood the processes of fixation and dehydration.

It is emphasized that the nuclear detail is readily evident only if the material is properly fixed and dehydrated, and if the hematoxylin stain is of the proper intensity. The nuclei are not distinguishable from any other nuclei if the stain is too deep, or if a light of low intensity is used, or if they are studied only with the low power objective of the microscope.

COMMENT

The techniques used give no information as to the nature or cause of this nuclear peculiarity which is common to the Walthard rest, the Brenner tumor, and certain of the pseudomucinous cystadenomas. A search of the literature dealing with Walthard rests and Brenner tumors reveals no mention of this detail of nuclear morphology. It appears not to be an artefact, since it is seen with such striking similarity not only in our own material, but in that obtained from two other laboratories, all three of which employ different fixing and dehydrating agents. It is possible that it may be due simply to folding. Why this should occur not only in the solid collections of cells, where folding might conceivably be due to crowding, but also in the cystic or semicystic rests and nests, where there is not the slightest evidence of nuclear

crowding, cannot be stated; nor can one state why cells such as these do not occur with greater frequency in other densely cellular tissues. The possibility therefore arises that these cells may be of a specific type, entirely separate and apart from any ovarian or tubal cells heretofore described. To be sure, one must consider such a possibility with caution, since similar cells may be seen in structures other than those herein considered. For example, isolated cells of like configuration may be found occasionally in the epithelium covering the mucosal folds of the Fallopian tube, in the ovarian stroma, and elsewhere. In addition, of 8 granulosa cell carcinomas examined, one contained several circumscribed areas made up of cells which were indistinguishable from those described here. One of the remaining 7 contained occasional such cells, whereas the cells making up the other 6 were of the characteristic granulosa cell type. In the latter, many of the cells were folded, but their outlines were sharply angulated and irregular, and of varying shape and size. In the first instance, the question arises as to whether the tumor may be of a mixed type, or whether, under certain circumstances, the cells making up the granulosa cell carcinoma may assume characteristics similar to those described. It is worthy of mention, however, that with the single exception of the tumor mentioned above, I have never seen these cells in such profusion or with precisely the same relationship to one another as in the tissues discussed here. Of incidental interest is the fact that the cells making up the rete ovarii and the epoophoron tubules are not of the basic type herein described. This might be considered as evidence against the hypothesis of Schiller that Brenner tumors may arise from these structures.

In discussing with various authorities the possibilities as to the identity of these cells, the most significant opinion received was that of Dr. A. C. Ivy, who calls attention to the striking similarity of the nuclei to those of Sertoli cells. Sertoli's cells, it will be recalled, are found in the epithelium of the seminiferous tubules of the adult testis. Their function is supportive and nutritive. They have no endocrine function, as evidenced especially by the fact that the seminiferous tubules of the cryptorchid testis are composed only of these cells. Of especial interest is the development of the Sertoli cells from indifferent epithelial cells of the undifferentiated embryonal gonad. Further exposition of the possible relationship of the basic cell type herein described to the Sertoli cell is beyond the scope of this paper. However, a course of investigation is suggested which may solve the riddle of the histogenesis of the Walthard rest, the Brenner tumor, and at least a portion of the pseudomucinous cystadenomas of the ovary.

SUMMARY AND CONCLUSIONS

Walthard rests are a common finding in the normal Fallopian tube. They occur, but appear to be less common, in the ovary.

Walthard rests and Brenner tumors bear a strong resemblance to one another, not only in intrinsic architecture, but also, and more especially, in nuclear detail. The basic nuclear type of each is readily identifiable by the presence of a median groove or fold. The deviations from this basic type are described. Though by no means limited to the tissues in question, this nuclear peculiarity is sufficiently constant to be regarded as a fundamental characteristic of both the Walthard rest and the Brenner tumor. Furthermore, its presence in both structures appears to strengthen the hypothesis that they may be derived from the same tissue. The similarity of this nucleus to that of the testicular Sertoli cell is worthy of note.

The presence of the basic nuclear type in many pseudomucinous cystadenomas is of interest in considering the possibility that a small proportion of these tumors may be derived from Brenner cell nests.

ADDENDUM: Since this paper was submitted, a fourth Brenner tumor has come to our notice. The patient was a 41-year-old Negress who complained of menorrhagia and metrorrhagia of two years' duration. Associated pathologic findings included fibromyomas of the uterus and salpingitis isthmica nodosa. The Brenner tumor was an incidental finding. The tumor measured 0.6 cm. in diameter, and was of the solid variety. The cellular detail conforms with the description given above.

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THE RELATIONSHIP BETWEEN LATE PRENATAL HEMOGLOBIN LEVELS AND FEBRILE PUERPERAL MORBIDITY

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THAT the course of the puerperium is influenced by the amount of blood lost at the time of delivery, has been emphasized by Peckham and Kuder,[1] Pastore,[2-4] and Reich,[5] among others. Pastore, whose work is of particular interest, found an association between the amount of blood lost in relation to the size of the individual and the post-partum blood cell volume. He found further a distinct relationship between each of these factors and the incidence of puerperal febrility. While he does not mention adjustments for complications, trauma, and operative interference, factors which may simultaneously affect both bleeding and exposure to infection, it is unlikely that his findings are explainable on this basis alone.

Assuming the post-partum physiologic concentration of the blood to be a fairly uniform process, any differences in the puerperal blood content would depend upon both the blood status at term and the blood loss experienced at delivery. The relationship between the extent of this loss and the occurrence of post-partum morbidity having been demonstrated by Pastore, the question arises whether the prenatal blood status, as routinely determined, shows a similar relationship to the puerperal course.

It has repeatedly been observed that, in a large proportion of all pregnancies, there is a definite decline in hemoglobin values, often to low levels. Opinions differ as to the extent that this is attributable to physiologic hydremia, on the one hand, or to true hypochromic anemia on the other. In any event, the functional capacity of the blood may well vary with its content per unit of volume, however, produced. The practical importance of examining this content, as a prenatal routine depends upon: (1) Is the information useful in the management of pregnancy? (2) May a simple procedure, such as a hemoglobin determination, serve as an index? The purpose of this study is to determine, if possible, whether the likelihood of post-partum fever varies with the ante-partum hemoglobin level, despite certain inaccuracies of the test, and regardless of the differing interpretations respecting anemia. The material reviewed is taken from the records of normal deliveries on the

obstetric service of the Johns Hopkins Hospital, over the three-year period, Sept. 1, 1937, to Aug. 31, 1940.

METHOD AND CONDITIONS OF STUDY

In view of the lack of uniformity in the prenatal records of private cases, these were considered unsuitable for the purpose. Since in primiparous labor trauma is quite varied and artificial delivery frequent, it seemed desirable also to limit the study to multiparas.

The routine prenatal practice of the clinic included hemoglobin readings (Sahli) at the time of registration, and again within the "last month." The "last month" reading falls actually within twenty-eight days of labor in only about one-half of the patients. In hospital deliveries blood loss was estimated or measured with about equal frequency. Checks indicated that estimates are approximate within 50 c.c. Blood loss in homes was almost always estimated. During the puerperium, temperature was recorded at four-hour intervals in the wards, and once daily in the home. Excluding the first day, if the temperature reached 100.4° F. or more on any two days, the case was coded as "febrile"; if on only one day, as "one-day fever."

Patients with abnormal conditions during pregnancy, possibly affecting both blood content and temperature, were excluded, as were patients who had premature labor, artificial delivery, induction, tamponade, and similar manipulations not fairly common to the entire group. Also discarded were afebrile patients whose records covered less than eight days, and patients receiving transfusion, except when given after the onset of fever. Because of marked differences in the incidence of fever in negro and white patients, the two were separately tabulated. Further separation was made between confinements in the home and in the hospital. Home cases were included since, in a dual service, the hospitalized group might not be completely representative of all patients enrolled.

This method of selection seems to provide a group of cases in each category that is reasonably homogeneous with respect to those obvious extrinsic variables which affect the probability of febrile puerperiums.

FINDINGS

The records of 2,018 consecutive, normal parous pregnancies, with spontaneous term deliveries, were selected and abstracted according to the foregoing definitions. They are distributed into four principal categories, with incidence rates of febrile puerperiums, as follows:

Hospital cases	470 negroes	51 febrile	10.9%
	520 whites	35 febrile	6.7%
Home cases	741 negroes	44 febrile	5.9%
	287 whites	9 febrile	3.1%
Total cases	2,018	139	6.9%

For each place of confinement, negroes experience febrile puerperiums about twice as frequently as do white individuals. This conforms to the experience covering all cases on this service. Among hospital patients, whose temperature is taken more frequently, the incidence of fever is double that for home patients of corresponding color, in this particular series. This differs in degree from the general experience of the service, where the ratio is about 5 to 1. The discrepancy is attributable to the exclusion, from the series, of complications and operative procedures.

It is felt that in general the late prenatal hemoglobin status is reasonably well evaluated if observations are made within four weeks of labor. In the series studied, record of such examination was found in 1,001 patients, about half of the total. In each of the four principal categories, comparisons of febrility rates for patients with known and with unknown hemoglobin levels showed no differences that were statistically significant. The sample of 1,001 cases may therefore be considered as representative of the whole group studied.

In Table I these 1,001 cases are divided by color, and distributed by grouped hemoglobin values. The distributions are obviously different as between white individuals and negroes. Less than 14 per cent of the

TABLE I. LATE GESTATIONAL HEMOGLOBIN GROUPING OF 1,001 NORMAL MULTIPARAS, SPECIFIC FOR COLOR

HEMOGLOBIN GRAMS PER 100 C.C.	NUMERICAL DISTRIBUTION		PER CENT DISTRIBUTION	
	WHITE	NEGRO	WHITE	NEGRO
6.5- 8.9	14	66	3.2	11.6
9.0- 9.9	45	106	10.4	18.7
10.0-10.9	117	200	27.0	35.2
11.0-11.9	111	137	25.6	24.1
12.0-14.5	146	59	33.7	10.4
Totals	433	568	99.9	100.0

TABLE II. PUERPERAL FEBRILITY RATES FOR VARYING LATE PRENATAL HEMOGLOBIN LEVELS

From records of 1,001 normal multiparas, spontaneous term deliveries, showing number of cases, and percentage with febrile puerperiums, according to place of confinement and hemoglobin values within last four weeks of gestation.

HEMOGLOBIN GRAMS PER 100 C.C.	HOSPITAL CASES		HOME CASES		TOTALS	
	NO. OF CASES	% FEBRILE	NO. OF CASES	% FEBRILE	NO. OF CASES	% FEBRILE
6.5- 8.4	22	27.3	21	14.3	43	20.9
8.5- 8.9	13	23.1	24	16.7	37	18.9
9.0- 9.4	36	16.7	47	8.5	83	12.0
9.5- 9.9	30	16.7	38	13.2	68	14.7
10.0-10.4	95	10.5	100	7.0	195	8.7
10.5-10.9	58	6.9	64	3.1	122	4.9
11.0-11.4	66	7.6	94	2.1	160	4.4
11.5-11.9	44	4.5	44	2.3	88	3.4
12.0-12.4	84	2.4	59	0.0	143	1.4
12.5-14.5	33	3.0	29	3.4	62	3.2
Totals	481	9.2	520	5.6	1,001	7.3

white patients had under 10.0 Gm. of hemoglobin per 100 c.c. of blood, as compared with 30 per cent of the negroes. Over three times the proportion of white patients as of negroes reached term with hemoglobin levels of 12.0 or higher.

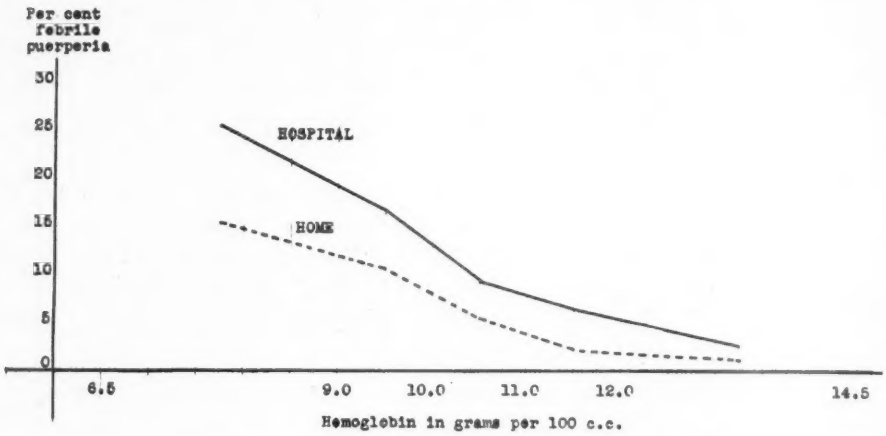

Fig. 1.—Relation of late prenatal hemoglobin level to puerperal febrility in 1,001 normal multiparas, by place of confinement (Table III).

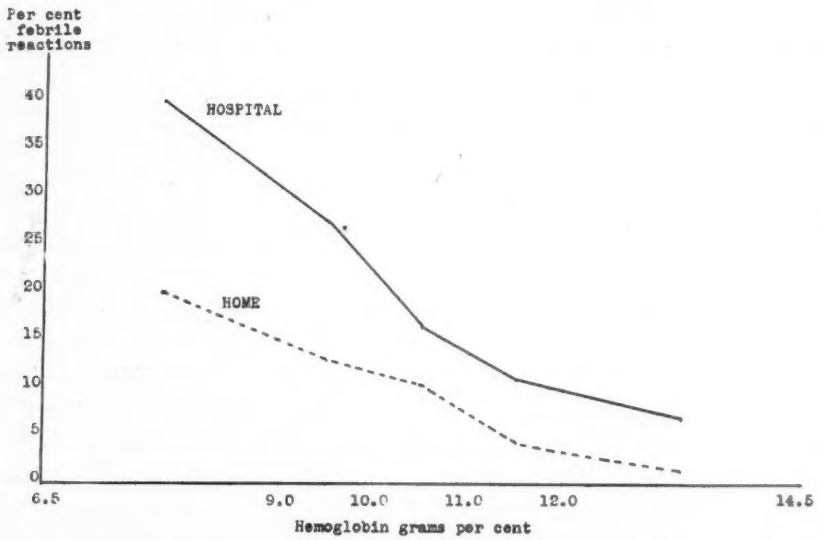

Fig. 2.—Relation of late prenatal hemoglobin level to puerperal febrile reactions, including "one-day fever" in 1,001 normal multiparas, by place of confinement (Table IV).

Table II shows the same sample distributed by place of confinement and by late prenatal hemoglobin levels, in one-half-gram steps, with the febrility rates for each subgroup. The marked decline of fever incidence with ascending blood values is shown graphically in Fig. 1. The same consistent relationship is reflected when the data are subdivided accord-

ing to color. Table III shows this analysis summarized by grouping the hemoglobin values into broader classes.

Summarizing these tabulations, those patients with prenatal hemoglobin values under 9.0 Gm. had febrility rates of 25.7 per cent in hospitals and 15.5 per cent in homes, whereas those with values of 12.0 Gm. or more had rates of 2.6 and 1.1 per cent, respectively. The incidence shows a consistent trend downward with ascending intermediate hemoglobin levels throughout all the tabulations. There are but rare interruptions, incident to small samples in the smaller subdivisions of Table II.

The sample was then examined to determine whether a relationship of this order is reflected by "febrile reaction" rates, when cases of "one-day fever" are added to those of conventionally defined morbidity. The analysis is given in Table IV and shown graphically in Fig. 2. Rates for corresponding hemoglobin levels differ from those of Table III in magnitude, but the internal arrangements are strikingly similar. Thus, either by the usual standard of puerperal febrility or by including all one-day fevers, the inverse relationship to late gestational hemoglobin content, per unit of blood, seems evident.

Especially noteworthy is the steady decline of febrility with ascending prenatal hemoglobin, between and beyond levels of 10.0 and 12.0 Gm., the range embracing values usually considered "satisfactory" or "normal."

The influence of blood loss at delivery is a factor that also must be considered. In these records bleeding is expressed in terms of absolute quantity, without regard to the size of the patient. The observation was recorded in 2,015 cases, of which 1,027 are home deliveries with estimated blood loss. Of 988 hospital deliveries, 60 per cent have estimates and 40 per cent have measurements. The proportion of measurement of blood loss was about the same among those of known and of unknown late hemoglobin status.

Febrility rates for varying amounts of blood loss at delivery are given in Table V. For comparison, the 396 hospital deliveries with measured blood loss are shown separately. Fever rates in this group closely approximate rates within the whole hospital group. For the purpose of separating cases into broad classes of blood loss, the inclusion of estimates seems acceptable.

There is no discernible trend of fever incidence with rising losses of blood in ranges below the "hemorrhage" level, but a marked rise occurs among patients suffering losses of 600 c.c. or more. Subdivision of the material by color, in this and in other tabulations, by steps of 50 c.c. and 100 c.c., did not alter the picture.

It thus appears that normal multiparas, spontaneously delivered under stable conditions regarding trauma and infection exposure, experience a distinctly increased risk of febrility following excessive bleeding, regardless of their hemoglobin status at term.

TABLE III. PUERPERAL FEBRILITY RATE FOR VARYING LEVELS OF LATE PRENATAL HEMOGLOBIN

Analysis, according to color and place of confinement, of 1,001 records of normal multiparas with spontaneous term deliveries, showing cases and incidence of febrile puerperiums by hemoglobin values grouped on a contracted scale

HEMOGLOBIN GRAMS PER 100 C.C.	HOSPITAL						HOME					
	WHITE		NEGRO		COMBINED		WHITE		NEGRO		COMBINED	
	NO. OF CASES	% FEBRILE	NO. OF CASES	% FEBRILE	NO. OF CASES	% FEBRILE	NO. OF CASES	% FEBRILE	NO. OF CASES	% FEBRILE	NO. OF CASES	% FEBRILE
6.5- 8.9	11	18.2	24	29.1	35	25.7	3	33.3	42	14.3	45	15.5
9.0- 9.9	33	15.1	33	18.2	66	16.7	12	8.3	73	10.9	85	10.6
10.0-10.9	71	7.0	82	11.0	153	9.2	46	4.3	118	5.9	164	5.5
11.0-11.9	63	6.4	47	6.4	110	6.4	48	2.1	90	2.2	138	2.2
12.0-14.5	92	2.2	25	4.0	117	2.6	54	0.0	34	2.9	88	1.1
Totals	270	6.7	211	12.3	481	9.2	163	3.1	357	6.7	520	5.6

TABLE IV. INCIDENCE OF PUERPERAL FEBRILE REACTIONS, INCLUDING ONE-DAY FEVER, FOR VARYING LEVELS OF LATE PRENATAL HEMOGLOBIN

Analysis of 1,001 normal multiparas with spontaneous term deliveries, by color, place of confinement, and hemoglobin values, showing number of cases and rates for febrile morbidity plus one-day fever

HEMOGLOBIN GRAMS PER 100 C.C.	HOSPITAL						HOME						TOTALS	
	WHITE		NEGRO		COMBINED		WHITE		NEGRO		COMBINED			
	NO. OF CASES	% FEBRILE	NO. OF CASES	% FEBRILE	NO. OF CASES	% FEBRILE	NO. OF CASES	% FEBRILE	NO. OF CASES	% FEBRILE	NO. OF CASES	% FEBRILE	NO. OF CASES	% FEBRILE
6.5- 8.9	11	27.3	24	45.8	35	40.0	3	33.3	42	19.0	45	20.0	80	28.8
9.0- 9.9	33	27.3	33	27.3	66	27.3	12	8.3	73	13.7	85	12.9	151	19.2
10.0-10.9	71	12.7	82	19.5	153	16.3	46	6.5	118	11.9	164	10.4	317	13.2
11.0-11.9	63	9.5	47	12.7	110	10.9	48	4.2	90	4.4	138	4.4	248	7.3
12.0-14.5	92	6.5	25	8.0	117	6.8	54	0.0	34	2.9	88	1.4	205	4.4
Totals	270	12.2	211	20.8	481	16.0	163	4.2	357	10.4	520	8.5	1,001	12.1

There were 32 patients who lost 600 c.c. or more of blood, only 23 of whom had hemoglobin determinations within four weeks prior to term. This number is too small, and the bleeding range too great (up to 1,500 c.c.) for subdivision according to hemoglobin levels, color, and place of confinement. Discarding these 23 cases, there remain 978 case records of normal multiparas of known late gestational blood status with spontaneous onset and termination of labor at term, experiencing blood losses of less than 600 c.c. These were analyzed as regards fever incidence in relation to both blood loss at delivery and the late prenatal hemoglobin level.

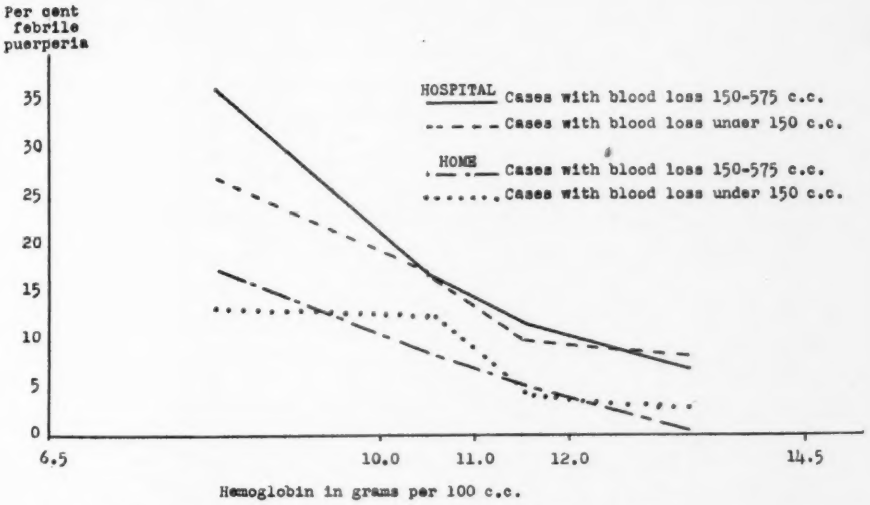

Fig. 3.—Relation of late prenatal hemoglobin level to puerperal febrility for cases in similar ranges of delivery blood loss from 467 hospital and 511 home deliveries. (Summary tabulation not shown.)

TABLE V. PUERPERAL FEBRILITY RATES FOR VARYING AMOUNTS OF BLOOD LOSS AT DELIVERY

From records of 2,015 normal multiparas with spontaneous term deliveries, showing number of cases and percentage febrile, by place of confinement, and amount of blood loss, estimated or measured*

BLOOD LOSS TO NEAREST 25 C.C.	HOSPITAL (MEASURED ONLY)*		HOSPITAL (MEASURED AND ESTIMATED)		HOME (ESTIMATED)*		TOTAL (MEASURED AND ESTIMATED)	
	NO. OF CASES	% FEBRILE	NO. OF CASES	% FEBRILE	NO. OF CASES	% FEBRILE	NO. OF CASES	% FEBRILE
0-125	149	8.1	527	8.0	569	4.7	1,096	6.3
150-275	133	9.0	294	9.9	332	4.5	626	7.0
300-425	74	8.1	116	6.9	92	8.7	208	7.7
450-575	25	0.0	31	3.2	22	4.5	53	3.8
600 and over	15	26.7	20	30.0	12	16.7	32	25.0
Totals	396	8.6	988	8.7	1,027	5.2	2,015	6.9

*Only occasional blood loss measured in home delivery. Measured in 40 per cent of *hospital* cases; shown in first column for comparison.

TABLE VI. PUERPERAL FEBRILITY RATES ACCORDING TO PRENATAL HEMOGLOBIN LEVEL AND EXTENT OF BLEEDING AT DELIVERY

From records of 978 normal multiparas, spontaneous term deliveries, with blood losses under 600 c.c., showing number of cases and percentage febrile, by color, place of confinement, amount of bleeding, and hemoglobin level in last month of gestation

HEMOGLOBIN GRAMS PER 100 C.C.	WHITE						NEGRO					
	BLOOD LOSS TO NEAREST 25 C.C.						BLOOD LOSS TO NEAREST 25 C.C.					
	0-125		150-575		TOTALS		0-125		150-575		TOTALS	
	NO. OF CASES	% FEBRILE	NO. OF CASES	% FEBRILE	NO. OF CASES	% FEBRILE	NO. OF CASES	% FEBRILE	NO. OF CASES	% FEBRILE	NO. OF CASES	% FEBRILE
Hospital Cases												
6.5- 9.9	23	13.0	21	19.0	44	15.9	33	15.1	23	30.4	56	21.4
10.0-10.9	32	9.4	39	5.1	71	7.0	40	12.5	40	10.0	80	11.2
11.0-11.9	28	3.6	32	6.2	60	5.0	24	4.2	20	10.0	44	6.8
12.0-14.5	40	2.5	47	2.1	87	2.3	11	9.1	14	0.0	25	4.0
Totals	123	6.5	139	6.5	262	6.5	108	11.1	97	13.4	205	12.2
Home Cases												
6.5- 9.9	8	12.5	7	14.3	15	13.3	68	10.3	45	13.3	113	11.5
10.0-10.9	21	9.5	24	0.0	45	4.4	59	6.8	58	5.2	117	6.0
11.0-11.9	21	4.8	25	0.0	46	2.2	51	2.0	39	2.6	90	2.2
12.0-14.5	24	0.0	28	0.0	52	0.0	20	5.0	13	0.0	33	3.0
Totals	74	5.4	84	1.2	158	3.2	198	6.6	155	6.5	353	6.5

The blood loss value of 150 c.c. is approximately the median for the group as a whole. The median hemoglobin value is 11.5 Gm. for white patients and 10.5 Gm. for negroes. The 978 were divided according to blood loss ranges above and below the median, and hemoglobin ranges embracing the two median values and the extremes in each direction. The numbers and corresponding rates are given in Table VI. Fig. 3 shows febrility by changing hemoglobin levels for patients with great and small blood losses, in hospital and at home.

Within like hemoglobin ranges, comparisons of fever rates by the extent of bleeding, in this and in other tabulations, fail to disclose a distinct pattern. The blood loss determinations if not entirely accurate are certainly adequate for establishing the broad limits used. Within the limits shown, and consistently throughout other subdivisions of blood loss, the inverse relationship of febrile puerperiums to late gestational hemoglobin is constant and distinct. This suggests that under comparable conditions of trauma and infection exposure, and in the absence of serious hemorrhage, the incidence of febrile morbidity is more closely related to the blood content at term than to the amount of bleeding incident to delivery.

Morbidity comparisons by color, for varying hemoglobin levels, may be made from Tables III and VI. Total negro rates, for each place of confinement, bear a two to one ratio to corresponding total white rates. This ratio exists in the total cases studied, and has long been observed in the general experience of the Service. Compared within similar hemoglobin ranges, however, the negro and white rates are more nearly equal, the ratios centering about 1.3 or 1.4 to 1. In Table I the negro and white cases have obviously different distributions into hemoglobin levels. Taken together, these findings suggest that the lower hemoglobin values prevailing among negroes account, in part, for the much greater incidence of febrile puerperiums which they experience.

SUMMARY

1. Records of 2,018 consecutive multiparas, with normal term pregnancies and spontaneous home or hospital deliveries, are reviewed. Conditions of trauma, infection exposure and handling were reasonably homogeneous for the group.

2. Hemoglobin determinations, within four weeks ante partum, were available in 1,001 cases. A marked, almost uninterrupted, decline of the incidence of febrility, with increasing values of hemoglobin, is reflected throughout various tabulations by color and place of confinement.

3. The rates of febrility based upon all febrile reactions, including "one-day fever," show a similar arrangement.

4. This relationship persists through and above a hemoglobin range ordinarily considered satisfactory.

5. Delivery blood loss was measured or estimated in 2,015 cases. For losses of 600 c.c. or more, fever rates were two to ten times the rates for lesser amounts of bleeding. Blood loss within "normal" ranges was not demonstrably related to febrility.

6. Patients with blood losses of less than 600 c.c., when subdivided according to prenatal hemoglobin levels and amounts of blood loss, present evidence that puerperal morbidity is related to the blood status at term, more closely than to bleeding at delivery, short of serious hemorrhage.

7. Racial comparisons of hemoglobin distribution, total fever rates, and rates within corresponding hemoglobin ranges, give evidence that the low prenatal blood values prevailing among negroes on this service are an important factor contributing to their much greater incidence of puerperal morbidity.

8. The findings indicate that an acid hematin test, during the last month of pregnancy, is a useful index of potential resistance to infection. They serve to emphasize the importance of hemoglobin determinations at intervals during pregnancy. Commonly encountered values between 10.0 and 12.0 Gm., whether "normal" or not, seem to express a status distinctly less satisfactory than higher levels. With due respect to the conservation of blood at delivery, the blood content with which a woman reaches term seems deserving of equally energetic attention.

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It has been repeatedly reported that the symptoms of an allergy in women tend to become aggravated before and during menstruation. Asthmatic symptoms, however, usually improve with the onset of the flow. This might be due to (1) increased general irritability, (2) possibility that patient is sensitive to progestin or theelin, or (3) that premenstrually the blood contains an increased amount or again abnormally low amount of certain hormones.

Blood estrogen determinations on 79 allergic patients showed a premenstrual relative estrogen deficiency in 63.3 per cent, compared with 4.7 per cent in 42 nonallergic women.

Administration of large doses of theelin and lipolutin premenstrually was of benefit only to a limited number of patients who had symptoms exclusively before and during menstruation.

Hugo Ehrenfest.

ABORTION IN RABBITS FED A VITAMIN K DEFICIENT DIET*

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EARLY in the modern investigations of hypoprothrombinemia, Brinkhous, Smith, and Warner showed that the blood of the newborn infant contains only a fraction of the prothrombin present in the blood of the adult. This observation has been repeatedly confirmed by all who have used the titration method of Warner, Brinkhous, and Smith for the determination of prothrombin (Javert and Moore, and Hellman and Shettles). Tests by the technique of Quick do not show this neonatal deficiency (Quick and Grossman). Both procedures reveal a fall in the level of prothrombin during the neonatal period, starting from six to forty-eight hours after birth and continuing for several days (Owen, Hoffman, Ziffren, and Smith).

In the original series of Brinkhous, Smith, and Warner, one infant with clinical hemorrhagic disease of the newborn infant had an extremely low level of prothrombin. Shortly after the time when vitamin K became available for clinical trial Waddell, Guerry, Bray, and Kelley found that the administration of vitamin K to two newborn infants with an abnormally high prothrombin time and clotting time gave a prompt and striking reduction of these two laboratory measurements of the bleeding tendency. They suggested that vitamin K should be a valuable therapeutic agent in hemorrhagic disease of the newborn infant. These findings were readily confirmed by many investigators, and it was further shown that the same elevation of the prothrombin of the infant was secured when the vitamin was given to the mother before delivery (Shettles, Delfs, and Hellman; Hellman, Moore, and Shettles). Of equal clinical importance was the observation by the above and other investigators (Waddell and Guerry, and Kugelmass) that the bleeding in clinical hemorrhagic disease of the newborn infant ceased on the administration of vitamin K.

From these investigations it may be concluded in broad terms that all newborn infants have a relative deficiency of prothrombin; that when this deficiency is excessive the parenchymatous bleeding of hemorrhagic disease of the newborn infant appears; and that the administration of vitamin K to the mother before delivery or to the infant after birth corrects the deficiency and prevents or stops the bleeding. It is possible that

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more precise study will reveal the role of other contributing or accessory etiologic factors, such as birth trauma, disease of the liver of the infant, and toxemia in the mother (Javert).

In the summer of 1938 as the above facts were beginning to unfold, it occurred to us that the production of hemorrhagic disease of the newborn in an experimental animal would give the investigator a more convenient and exact method by which to study this disease. Reports in two publications gave encouragement that the project was feasible. First, Moore, Brodie, and Hope showed that the newborn pups of rats fed a diet deficient in certain elements of the B complex died soon after birth, and that there were hemorrhages in the viscera and in the subcutaneous tissues. Second, in the calves of cows with sweet clover disease, there was abundant evidence of hemorrhage and at times it was sufficiently severe to lead to death (Roderick and Schalk).

The original purpose of the experiment, the production, and study of experimental hemorrhagic disease of the newborn was a complete failure, but the unexpected finding of abortion in all animals on a vitamin K deficient diet justifies a full report. The rabbit was selected as the experimental animal because of the ease of breeding, the relatively short period of gestation and the size of the animal. The latter point was important, as the withdrawal of considerable amounts of blood was necessary to follow the level of the plasma prothrombin. The artificial diet was based on the principles followed by Goldblatt and Moritz in their study of avitaminosis D in the rabbit. There was a vitamin-free source of protein, carbohydrate, and fat. Minerals, vitamins, and other materials were added to these basic constituents. The diets used in the two experiments to be reported were different and are designated R-2 and R-3.

DIET R-2 (FIRST EXPERIMENT)

Dried egg white	150
Wheat starch	375
Cottonseed oil	112.5
Salts (McCollum 165)	32.5
Yeast (extracted with acetone in Soxhlet for 8 hours)	32.5
Agar	32.5
Cod-liver oil	15
Alfalfa powder (extracted with acetone in Soxhlet for 24 hours)	750
Water	to proper consistency
Germinated wheat oil	1 drop per day
Cevitamic acid	5 mg. per day

Diet R-3, used in the second experiment, was the same except that casein extracted with acetone for eight hours in a Soxhlet was substituted for the dried egg white. All of the materials except the wheat oil and cevitamic acid were thoroughly mixed, made into a dough with water and dried as pellets. Most of the rabbits ate the diet, but a few had to be

fed for the first few days at the beginning of an experiment. The ascorbic acid and wheat germ oil were fed with a pipette in the quantities indicated. The agar served to prevent diarrhea and the alfalfa was a source of roughage. The control animals received the same diet except that the alfalfa was not extracted. At intervals, the plasma prothrombin was determined according to the technique of Warner, Brinkhous, and Smith.

The first experiments on 6 rabbits were conducted at Cornell University Medical College during 1938 and 1939, and the second group of four animals were studied at the Washington University School of Medicine in 1939 and 1940.

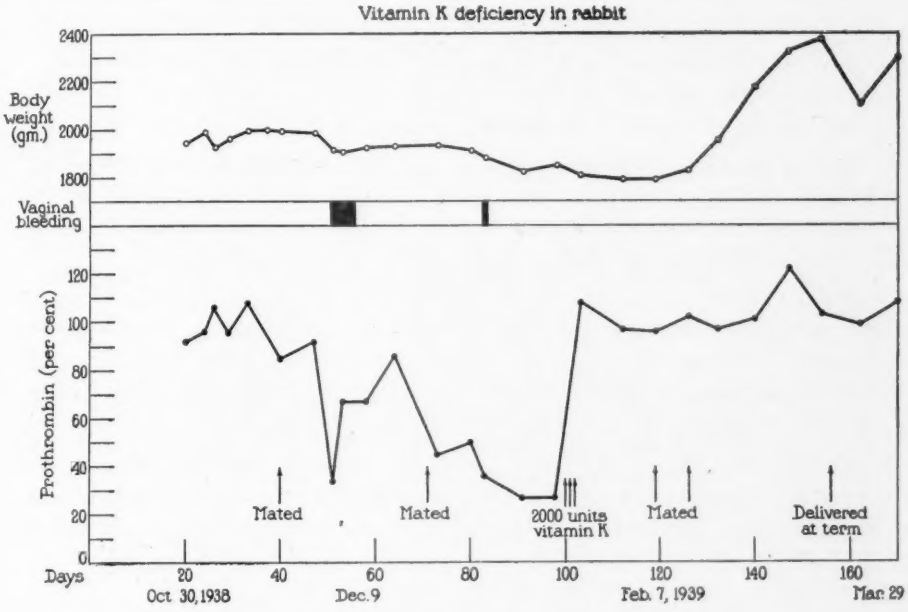

Fig. 1.

FIRST EXPERIMENT

Six rabbits, four Dutch and two Beveran, all of which had carried a normal pregnancy to term before the experiment, were placed on the artificial diet. Two animals served as controls and were given the same diet except that the alfalfa was not extracted. Four animals received the vitamin K deficient diet. The cages were provided with false floors. At the end of 40 days all animals were mated with a male of the same breed. The two control animals had a normal pregnancy. On the tenth to the fourteenth day following mating, vaginal bleeding occurred in the four experimental animals and persisted for two to four days. Fetuses and placentas were recovered from three animals, while in one they were either retained or eaten by the mother. After a period of three weeks, the animals were again mated and again all aborted on the tenth to fourteenth day. During the same time period, the two control

animals went through a second normal pregnancy. One experimental animal was mated a third time and at the onset of the vaginal bleeding on the eleventh day, a hysterectomy was performed in order to secure material for histologic studies. One animal died two days after the onset of bleeding of the second abortion. The remaining two experimental animals, which had been on the diet for one hundred days and aborted twice, were given 2,000 units of klotogen on each of three days and then bred on the one hundred and tenth day. The artificial diet was maintained, except that these animals now received the same mixture as the control animals. Both matings resulted in a normal pregnancy with 5 to 6 living pups.

The plasma prothrombin in the experimental animals fell progressively, with a maximal decrease of 79 units or to 75 per cent of the original values. When abortion occurred, the determinations were always less than 35 per cent of normal. Following the administration of klotogen, the prothrombin returned to normal within three days. The results in one animal are shown graphically in Fig. 1.

SECOND EXPERIMENT

In the summer of 1939, synthetic pure chemical substances with great biologic activity as vitamin K became available; and it was decided that the experiments should be repeated under better conditions of control.

Four Dutch rabbits were placed in wire bottom cages and fed the deficient diet designated R-3. An oily solution of 2-methyl-1,4-naphthoquinone was given in doses of 1 mg. in 0.2 c.c. of oil every other day. After from twenty to thirty days all animals were mated and a normal pregnancy resulted. The young were destroyed and the mothers were continued on the deficient diet without the added 2-methyl-1,4-naphthoquinone. After forty days of this regime the animals were mated. On the ninth day all aborted. Placentas were recovered from two animals. After two to three weeks, a second pregnancy during the feeding of the deficient diet was initiated. All animals aborted on the eighth to the eleventh day, and two animals died in the succeeding week on the third and seventh day after the appearance of vaginal bleeding. Both were emaciated. The remaining two animals were given the same doses of 2-methyl-1,4-naphthoquinone as in the pre-experimental period and mated on the twentieth and twenty-fifth day. A normal term pregnancy with live pups resulted in both.

Prothrombin determinations in this experiment were confined to two values during each of the three periods, pre-experimental, experimental, and postexperimental, to establish that there was a normal value in the first and last and a low value in the second.

PATHOLOGIC CHANGES IN THE PLACENTAS

As noted above, placentas from 3 abortions in the first experiment and 2 in the second were recovered, fixed and sectioned. A composite description is as follows:

Sections of the placenta appeared to be normal except for the decidual plate. In all the sections there was hemorrhage in the decidual plate. These areas of hemorrhage were both recent and old. In the recent areas, the red cells appeared normal; in the older areas they had become decolorized; and in the still older areas the blood clot had been replaced

by laminated fibrin. There was not enough decidua present in any of the sections to determine the exact site of origin of these hemorrhages. However, this lesion was microscopically identical to that seen in retroplacental hemorrhage associated with human abortion.

DISCUSSION

Although the experiments comprehend only a relatively few animals the constancy of the results in all animals on two different occasions clearly indicates a relation between vitamin K deficiency and abortion in rabbits during the late first and early second trimester. The known effect of vitamin K deficiency in the production of hemorrhage and the finding of retroplacental hemorrhage in the rabbits point to the same conclusion. The fact that hemorrhage occurred at this point and not at other points in the body and that the plasma prothrombin had not fallen to the so-called critical levels of 10 to 25 per cent, suggests that the placenta is unusually susceptible to deprivation of vitamin K.

The adequate supply of vitamins A, B, C, D, and E in both experiments would appear to eliminate them as a cause of the pathologic change. Great care was taken to see that all animals received vitamin E, because of the known relation to reproduction and fetal resorption. The absence of abortions in the postexperimental period of the second experiments gives direct evidence that the deficiency was due to vitamin K.

Whether or not vitamin K deficiency is the cause of abortion in women cannot be ascertained from the facts at hand. The report of Javert is suggestive. In one patient with retroplacental hemorrhage, the cord blood contained only 13 per cent of normal prothrombin, but the mother's prothrombin was normal. Any further conclusions must await a comprehensive study of prothrombin before, during, and after abortion in a large number of women.

CONCLUSIONS

Vitamin K deficiency and hypoprothrombinemia in pregnant rabbits result in abortion at the end of the first trimester of gestation. The application of this observation to the study and treatment of abortion in women must await further study.

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THE ANOVULATORY FACTOR IN STERILITY*

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THE increasing use of endometrial biopsies in recent years has focused considerable attention upon the anovulatory factor in sterility. Recently we have taken endometrial biopsies from a number of sterility patients in the immediate premenstrual interval to determine the presence, or absence, of ovulation. Initial examination of 42 cases in this manner showed normal ovulation in 62 per cent (26 patients), and absence of ovulation in 38 per cent (16 patients). Critical examination of the ordinary clinical data on these anovulatory patients failed to show any findings, other than endometrial biopsy, to suggest an absence of ovulation. The incidence of anovulatory menstruation in sterility patients has been recorded by the following observers: 33 per cent, Mazer and Israel;[6] 29 per cent, Siegler;[11] 25 per cent, Jeffcoate;[4] 36 per cent, Kotz and Parker;[5] and 48 per cent, Novak.[7] Rock, Bartlett, and Matson[9] found in a series of 392 sterile patients that 9 per cent had an occasional anovulatory period, and that 4 per cent were habitually anovulatory. This emphasizes the need for more than one endometrial biopsy before judging a patient to be persistently anovulatory.

Our report deals with the effects of pregnant mare serum injections into anovulatory sterile patients who presented no gross pathologic findings. It was possible to give pregnant mare serum injections to 8 of the 16 anovulatory sterile patients in this series. Repeated endometrial biopsies were used before and after the injections to give controlled evidence of the therapeutic results. These showed evidence of ovulation after pregnant mare serum injections in 7 of 8 proved anovulatory patients. Only one pregnancy resulted in this anovulatory group, and this one terminated in an early miscarriage. It is unfair to blame this relative absence of pregnancy entirely upon the gonadotropic agent,

*Presented as a Scientific Exhibit at Michigan State Medical Society, Grand Rapids, September, 1941.

since all of the other important sterility factors were controllable in only 3 of these 8 anovulatory patients. The essential clinical facts are listed in summarized form by the following case reports.

CASE 1.—Patient, aged 22 years, married two and one-half years, had an early spontaneous miscarriage six months after marriage. No contraception and no pregnancy since that time. Menses were regular twenty-eight to thirty-day interval, and of six-days' duration. Endometrial biopsy, taken in premenstrual stage, showed proliferative type with no ovulation. Mare serum was given in dosage of 400 i. u. on the twelfth day, and 600 i. u. on the fourteenth day. Endometrial biopsy on the twenty-second day showed evidence of ovulation.

CASE 2.—Patient, aged 28 years, married four and one-half years, had used no contraception and had had no pregnancy. Menses were regular twenty-eight-day type. Duration of flow was normally seven days, but for last year periods had lasted ten to fourteen days in profuse amount. Premenstrual endometrium showed no evidence of ovulation. Mare serum was given: 400 i. u. on tenth day, and repeated on the twelfth day. Endometrial biopsy on the nineteenth day of the cycle showed no evidence of ovulation. This treatment was repeated for a total of three months without producing ovulation. The menorrhagia disappeared during the course of the above treatment.

CASE 3.—Patient, aged 30 years, married four years, had used no contraception and no pregnancy had occurred. Menses were always irregular with interval varying between three and twelve weeks. Premenstrual endometrium showed dilated tubular acini with no ovulation. Mare serum was used as 400 i. u. on the tenth day and 800 i. u. on the twelfth day. Biopsy one week later showed no ovulation. Treatment with mare serum was repeated during the next month on the tenth and twelfth day of the cycle, 800 i. u. on each day. Premenstrual biopsy again showed no ovulation. This same dosage was used during the next month and premenstrual endometrial examination showed ovulation to have occurred this time.

CASE 4.—Patient, aged 30 years, married five years, had used no contraception for last three years and had had no pregnancy. Menses regular with twenty-six to twenty-eight-day interval. Endometrial biopsy on twenty-second day of the cycle showed no ovulation. Mare serum was given: 400 i. u. on the twelfth day and 800 i. u. on the fourteenth day. Biopsy one week later showed the presence of ovulation. Further sterility factors discovered were closed tubes and nonmotile sperms.

CASE 5.—Patient, aged 25 years, married 4 years, had used no contraception for three years and had had no pregnancy. Menses were irregular every four to eight weeks. Six premenstrual endometrial biopsies between 1938 and 1940 showed no ovulation. Mare serum was used: 400 i. u. on the eleventh day and 800 i. u. on the thirteenth day. Biopsy one week later showed a secretory endometrium (Fig. 1). Mare serum therapy was continued until pregnancy resulted after two months of treatment. Miscarriage occurred after three months' amenorrhea.

CASE 6.—Patient, aged 29 years, had used no contraception and had had no pregnancy during three years of marriage. Premenstrual biopsy showed no ovulation. Mare serum injections were given: 400 i. u. each

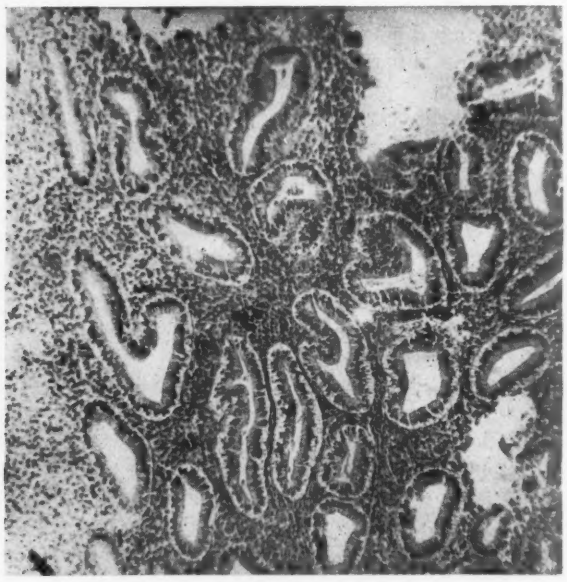

Fig. 1.

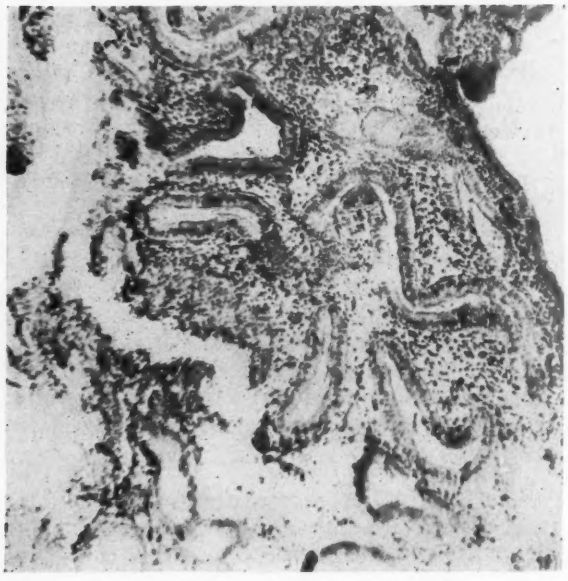

Fig. 2.

on the eleventh and fourteenth day. No ovulation was produced during the first month of this treatment, but evidence of ovulation was found following the second course of injections (Fig. 2).

CASE 7.—Patient, aged 39 years, had 2 pregnancies soon after the first marriage, fifteen years previously. There had been no pregnancy since second marriage, 2 years ago. Menses were regular and normal. Premenstrual endometrial biopsy showed no evidence of ovulation. Mare serum used: 400 i. u. each on the ninth and twelfth day. Biopsy of endometrium one week later showed ovulation to have occurred following these injections.

CASE 8.—Patient, aged 35 years, had been married ten years but had had no pregnancy. Menses were usually of twenty-eight-day interval, but occasionally missed one period. Several biopsies taken in the premenstrual interval showed no ovulation. Mare serum was used in dosage of 400 i. u. each on the twelfth and fourteenth days. Biopsy one week later showed evidence of ovulation.

DISCUSSION

A critical analysis of these case reports brings up some interesting considerations. Novak[8] expresses the almost universally accepted opinion that endometrial biopsy is the most reliable indicator of ovulation. However, Hamblen[2] states that ovulation may be present in an occasional case, evidenced by the presence of sodium pregnanediol glycuronidate in the urine, without the usual biopsy findings due to a refractory condition of the endometrium. While further work will settle this question, the preponderance of opinion at this time favors the view that endometrial biopsy gives correct information regarding ovulation. The first endometrial change after ovulation consists in a ranging into line of the nuclei of the gland cells. This process has been described by Hisaw,[3] Sturgis and Meigs,[12] Kotz and Parker,[5] Rock,[10] Novak,[8] Campbell, Lendrum, and Sevringhaus,[1] and others. Under the estrogenic influence of the proliferative phase the nuclei of the gland cells are situated at irregular levels with respect to the bases of the cells. With the advent of the lutein influence immediately after ovulation, it is commonly believed that this change is reflected in the endometrium by a ranging into line of these nuclei at a level somewhat near the centers of the cells. The clear spaces below this regular line of nuclei consist of glycogen granules, demonstrable by Best's carmine stain. Some observers (Novak,[8] Rock[10]) have noted a tendency for the gland cell nuclei to range into line and undergo mobilization in castrate patients treated with estrogenic substances. Rock has stated further that the nuclear changes in such cases are patchy and lack the uniformity seen in cases where ovulation has occurred. Our experience has included some 600 endometrial biopsies from patients with a variety of gynecologic conditions. Complete clinical diagnosis and follow-up were possible since this material came from private patients entirely. Correlation of biopsy and clinical findings leads us to support the view that endometrial biopsy is a reliable indicator of ovulation, and that the earliest microscopic sign of ovulation consists in a ranging into line and mobilization of the nuclei in the endometrial gland cells.

SUMMARY

Pregnant mare serum injections were followed by ovulation in 7 of 8 anovulatory patients, evidenced by endometrial biopsies taken before and after the gonadotropic treatment.

The authors wish to acknowledge their thanks to the Schering Corporation and to the Upjohn Company for the mare serum hormone used in these studies. The injection dosage is expressed in international units on the basis that 10 Cartland-Nelson units (gonadogen, Upjohn Co.) are equivalent to 200 international units (anteron, Schering Corporation).

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MALIGNANCY OF THE VULVA

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MALIGNANCY of the vulva is a comparatively rare disease.[1] At the Free Hospital for Women between January, 1890, and January, 1941, 66 cases have been seen. In the same interval there were 1,668 cases of carcinoma of the cervix, 475 of the body of the uterus, 179 of the ovary, and 562 of the breast. During this period there have been approximately 32,511 hospital admissions, making the incidence of carcinoma of the vulva 0.2 per cent in this gynecologic clinic.

Ages.—The youngest patient with malignancy of the vulva was 37 years of age, the oldest 85. All but 11 patients were over 50 years of age, the average being 60.5 years. This average age is five years higher than that of 100 women on whom superficial vulvectomies were performed for leucoplakia and kraurosis of the vulva,[2] lesions considered as precursors to carcinoma of the vulva.[3]

Location.—Of the 66 cases, the malignancy arose from the labia in 39 instances, usually on a leucoplakic base, but in one instance the seat of origin was a hidradenoma. The growth was sufficiently extensive to involve both sides of the vulva in 15 cases. In 24 cases it was unilateral, being present 12 times equally on each side. Malignancy was located

about the urethra in 9 cases. Since it is impossible in most instances to determine conclusively whether the cancer started in the urethra and spread outward, or began in the vulva and grew into the urethra, these 9 cases have been included as vulva cancer. In 10 patients the clitoris was the chief area involved. Bartholin's gland was included in the tumor on 4 occasions although an adenocarcinoma was present in only 1 of them. In 2 cases the disease commenced on the perineum at the fourchette. Venereal warts were associated with the disease in one of the perineal and one of the labial cases. Two of the patients had had vulvectomies elsewhere, and on admission to this Hospital had groin involvement, although the original lesion was absent.

Symptoms and Duration.—Multiple complaints were common. The most frequent one, however, was that of a growth in the vulva region. This occurred 44 times; on 28 occasions it was described as a "lump" and on 16 as an "ulcer." Irritation was the complaint 32 times and was mentioned as itching in 21 instances and burning and smarting in 11 others. Bleeding was associated in 18 cases although it was the chief complaint in only 5. Ten patients were bothered by dysuria, but in only 1 case was it the presenting symptom. Leucorrhea was the only complaint on 1 occasion but was mentioned in 4 others.

The duration of symptoms before the patient sought medical advice is appalling. Only 4 patients presented themselves in less than one month from the time of onset and only 1 of these had an early lesion. She was a patient who was being followed in this clinic after treatment for a carcinoma of the cervix. Forty patients presented themselves in less than a year from the beginning of symptoms, but of these only 27 were seen in less than six months and 15 in less than three. Nineteen patients had had difficulties for more than a year and 14 of these for more than two years. In 7 the history was indefinite. Thus only one-third had reported in less than six months while another third had had symptoms for more than a year. Itching and smarting of the vulva as well as persistent tumors and ulcers should be stressed as danger signals in cancer of the vulva. Too often, patients feel that itching is something of which they should be ashamed and hesitate to be examined. Moreover, local applications are hopefully indulged in over too long a period.

Pathology.—In this series there were found 1 fibrosarcoma, 1 hemangiosarcoma, and 1 lymphoblastoma of the vulva.* The remainder of the cases were carcinoma, a pathologic diagnosis having been established in all but 5 instances. Of the latter, 2 were moribund on entering the hospital, 3 had no biopsies, but the diagnosis was clinically unmistakable since they died of the disease, 2 within seven months and 1 within three years.

Of the 58 patients in whom cancer was diagnosed microscopically, 56 had epidermoid carcinoma and 2 adenocarcinoma. Either leucoplakia or kraurosis or both were found microscopically in conjunction with the cancer in 38, or 54.5 per cent. Both leucoplakia and kraurosis were present in 25 cases; the former alone in 9, and the latter alone in 2.

*Lymphoblastoma of the vulva is very rare.[4] This case has been mentioned in Graves, *Gynecology*, Edition IV, 1928, and at that time was believed to be the only case reported in the literature. The slide was examined by Drs. Frank B. Mallory, James Ewing, and S. B. Wolbach. Taussig, however, in 1937, reported a lymphosarcoma of the clitoris.[5]

Our patient when first seen was 43 years old. She had several tumors in the vicinity of the clitoris, the largest measuring 10 by 7.5 by 8 cm. A complete vulvectomy was performed in 1927. A short time later she received x-ray therapy in another city. In 1941 she was enjoying perfect health.

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An attempt to grade the cases according to the degree of malignancy was made. This was based largely on the number of mitoses and the tendency to form epithelial pearls. However, it was most unsatisfactory. Except for the general appearance of invasiveness which was influenced by the duration of the disease, there was no marked variation. Metastases appeared in the groins regardless of the degree of malignancy. There was no apparent prognostic significance, the extent of the disease when first seen and the general condition or age of the patient being far more important considerations.

Treatment and Results.—End results are presented on 54 cases which were seen prior to January, 1937, including 7 patients who had been operated upon at other hospitals. This allows for the conventional five-year follow-up. There was a five-year salvage of 15, or 27.7 per cent. For the 47 consecutive cases which had not received previous operative treatment at other hospitals, the salvage was 29.7 per cent. All patients lost were counted dead and all those who had died of any cause whatsoever were considered to have died of cancer.

As may be seen in Table I, many forms of treatment were employed in these 54 cases. The extent of the disease and the condition of the patient were the deciding factors.

TABLE I. FIVE-YEAR SURVIVALS

TREATMENT	NO. OF CASES	SURVIVALS	LOST	DEAD	% OF SURVIVALS
None	4	0	1	3	0
Radium alone	6	0	0	6	0
Radium plus bilateral groin dissection	1	0	0	1	0
Radium plus partial vulvectomy	3	1	0	2	33.3
Partial vulvectomy	5	0	4	1	0
Complete vulvectomy	14	5	1	8	35.6
Complete vulvectomy plus unilateral groin dissection	3	0	0	3	0
Complete vulvectomy plus bilateral groin dissection	9	5	2	2	55.5
Amputation of clitoris plus radium	1	0	1	0	0
Amputation of clitoris	1	0	1	0	0
Excision of urethra plus partial vulvectomy	1	1	0	0	100.0
Excision of tumor plus unilateral groin dissection	3	1	0	2	33.3
Excision of tumor plus bilateral groin dissection	3	2	0	1	66.6
Total	54	15	9	30	27.7

Four patients were not operated upon and all died. Of these, three were moribund on admission and the fourth refused treatment.

Radium was used as part of the initial treatment of 10 patients. On 6 of them it was the only therapy and on the 4 others it was used in conjunction with operation. The disease was advanced in all cases. There was only one survivor and this was a surgical case. The lives of 4 others were perhaps prolonged by the use of radium, since they lived from two to three years.

Partial vulvectomy or local excision was performed 11 times, 4 being in conjunction with radium. Of these there were 2, or 18.1 per cent, five-year survivors.

Complete vulvectomy alone was performed 14 times. Five patients, or 35.6 per cent, were considered cured.

Of 9 cases in which a bilateral groin dissection in addition to a complete vulvectomy was done 5, or 55.6 per cent, lived for five years. Four patients had the vulva and the groins operated upon in 1 stage and 5 in 2 stages with an interval of approximately one month between. Metastases were discovered in the groins in 5 cases. One of the 5, or 20 per cent, survived for five years. Of the cases in which no glandular involvement was found, 3, or 75 per cent, were known to be living and the fourth was thought by relatives to be alive, but could not be traced. She is counted as dead.

In 3 instances the local area was removed and the groin on one side dissected. One, or 33.3 per cent, survived.

In 3 others the local area including the growth was removed without doing a complete vulvectomy, but a bilateral groin dissection was performed as well. Two, or 66.6 per cent, survived.

Although extravagant conclusions cannot be made from a small number of cases, it would appear that groin dissections are important. In most instances a wide vulvectomy plus a bilateral groin dissection (i.e., the Basset operation) should be done, but often the disease is too advanced or the patients are in too poor condition. Many of them are elderly. If the procedure is carried out in two stages, however, it is not particularly shocking. This method tends to prevent hurry and allows for a more complete groin dissection. Moreover, if the wounds become septic postoperatively, there is not such a large gaping area to granulate. In removing the vulva, the use of the diathermy knife is helpful in reducing the amount of blood loss.

Operative Mortality.—Of the 66 patients, 4 were untreated and 7 received radiation alone. Of the 55 patients subjected to surgery in one form or another, 3 died postoperatively, a mortality rate of 5.4 per cent. Two patients died of a pulmonary embolism on the sixth and fifteenth days, respectively. Both deaths followed a vulvectomy. One died on the operating table, a bilateral groin dissection and an excision of one labium having been completed.

Secondary Operations.—Of the 54 patients seen prior to 1937, 5 had further treatment for recurrent disease, other than radiation alone; one had a local recurrence excised two years after her first operation here and thirteen years after the original operation for carcinoma of the vulva at another hospital. She was well three years after the last operation. Another patient had a local excision of the disease plus radium. Three patients had groin dissections at a late date, 2 of them having radium as well. All except the first patient are dead. To be of value, groin dissections must be done as near the time of the vulvectomy as possible, certainly within a month.

Gland Involvement.—In 19 patients who subsequently had an exploration of the groins, a definite preoperative statement was made as to whether metastasis would be found. In 9 the nodes were expected to be malignant and found to be negative in 5. In 10 that were thought to be negative preoperatively, 3 were found to be positive. Thus a correct

clinical diagnosis was made in only a little over 50 per cent. This further substantiates the importance of doing groin dissections.

Radiation.—Of the 66 patients, 21 have been treated with radium. In 6 it was the only form of therapy, since they were advanced cases, and 3 of them had been operated upon elsewhere first. In 8, it was used in conjunction with surgery and to 7 others it was administered for recurrent disease. Of the 21 cases, 4 received more than one application. The total dosage varied between 200 and 4,800 mg. hours, the usual dose being 1,500 to 1,600. There was only one 5-year survivor, and this patient had a wide local excision of the growth as well. In 8 patients, or more than one-third, it was followed by intense pain or sloughing. The larger the dose, the greater was the likelihood that pain would occur, but 1,600 mg. hours in one case and 2,000 in another were enough to cause pain. Except for 5 cases in which the radium was directed to the groins for metastatic disease, it was applied exclusively to the vulva. Thus on the whole radium has been unsatisfactory.

X-radiation was used on 18 cases, 6 times in conjunction with radium. Five times it was directed at the groins only, once at the groin and the vulva, and the remainder at the vulva alone. It was used in conjunction with operation in all but 3 cases; in one it was the only form of therapy, but with the other two radium was used as well. When the groins were radiated, no untoward effects were noted. When the vulva was treated, the burning and pain was similar to that which followed the use of radium in the same region. Its effectiveness is hard to estimate, since comparable cases with and without x-radiation were few. The dosage used varied between 800 and 3,200 r., but approximately 1,600 r. was the usual dose. It seems unwise to use it routinely on the vulva because of the pain that often accompanies it; but on the groins, it does little harm and may be of value.

CONCLUSIONS

1. Malignancy of the vulva is an uncommon disease occurring in 0.2 per cent of the patients at the Free Hospital for Women.

2. It is a disease primarily of women past the age of 50, but may occur in the relatively young.

3. In the majority of cases it is associated with leucoplakia and kraurosis of the vulva. Chronic Bartholinitis, or venereal warts, may be predisposing factors.

4. Epidermoid carcinoma is the usual pathologic picture. Adenocarcinoma or sarcoma is occasionally the type of malignancy. Classification of the degree of malignancy does not seem very helpful from a prognostic point of view.

5. Knowledge of the disease should be more widely disseminated, as the interval between the onset of symptoms and the time of entry into the hospital is too long.

6. For all patients entering this hospital, the five-year salvage is 27.7 per cent. If the patients previously operated upon at other hospitals for the disease are excluded, the total salvage is 29.7 per cent. The operative mortality is 5.4 per cent.

7. Although many forms of therapy have been resorted to, the treatment of choice is a radical vulvectomy plus a bilateral groin dissection. This is dependent on the extent of the disease and the general condition of the patient when first seen. When this is done the prognosis for five-year survival becomes 55.5 per cent.

8. Radiation to the vulva should be used only as a last resort. Either radium or x-ray causes marked discomfort in about one-third of the patients.

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MESODERMAL MIXED TUMORS OF THE BODY OF THE UTERUS

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MESODERMAL mixed tumors of the uterus and vagina are extremely rare and highly malignant neoplasms. Since their gross appearance, age incidence, and manner of attachment, when they arise in the body of the uterus, differ so strikingly from similar tumors of the cervix uteri and vagina, it was deemed expedient to confine this study to mesodermal mixed tumors of the body of the uterus.

Weber[16] reported the first case in the cervix uteri in 1867 and Anderson-Edmonnson (quoted by Kehrer[7]) described the first case in the body of the uterus in 1870. The term mesodermal mixed tumor was proposed by Kehrer[7] and supported by R. Meyer.[12a] Pfannenstiel[15] employed the term "traubiges Sarkom" or botryoid sarcoma, as it is known in this country, because of the grapelike character of the tumor when it had its origin from the cervix or vagina. This term has been discarded because a botryoid appearance is not a constant characteristic of these tumors, especially when they arise in the body of the uterus.

In a recent publication[10] I collaborated with R. J. Lebowich in a critical analysis of the literature on mesodermal mixed tumors of the body of the uterus. In this study 12 genuine cases were collected, following the pathologic criteria of Läwen,[9] and an additional case was reported. Since this study 2 papers have been published dealing with mesodermal mixed tumors of the body of the uterus. Although the case of Glass and Goldsmith[4] presented clinical and pathologic characteristics of a mesodermal mixed tumor, it is unacceptable. The bulk of the tumor consisted of smooth muscle, cartilage, and mucoid tissue, but no true embryonal myoblasts or cross-striated muscle tissue were demonstrated.

Three cases were described by Liebow and Tennant,[11] but only one of their cases contained striated embryonic muscle tissue, in addition to other heterotopic mesodermal elements. This brings the number of acceptable reported cases to 14.

CASE REPORT

M. G., a 55-year-old, Russian born, white housewife was admitted into the Beth Israel Hospital on Feb. 16, 1941, complaining of vaginal bleeding of three months' duration. The family history was irrelevant. The patient had suffered with "piles" for many years. About 7 years ago she was treated for dysuria and frequency of urination. She has had 2 children, the last childbirth occurring twenty-eight years previously. An uneventful menopause occurred three years ago.

For the past three months the patient had noticed intermittent vaginal bleeding. This had not been progressive in character. There had been no vaginal discharge in the intervals between bleeding episodes. A history of abdominal pain, urinary or rectal disturbances was not elicited.

A short, soft, systolic murmur was audible in the region of the cardiac apex. The systolic blood pressure was 142 mm. and the diastolic 78 mm. The lungs were clear to percussion and auscultation. Upon deep abdominal palpation a mass could be felt in the midline just above the symphysis pubis.

Vaginal examination revealed a uterus enlarged to the size of a three months' gestation, symmetrical and freely movable. Protruding from the external os was a polypoid mass of tissue; when the mass was grasped with a tenaculum, the tissue tore easily, leaving a raw, ragged, freely bleeding surface.

Laboratory Data.—Urine: specific gravity, 1.022; acid; albumen, 2-plus; sugar, negative; 1 to 2 white blood count per high power field. Hematologic: Hg (Sahli), 98 per cent; red blood count, 4,000,000; white blood count, 11,400. Differential smear: polymorphonuclear leucocytes, 65 per cent; lymphocytes, 25 per cent; monocytes, 10 per cent. Complement fixation test for syphilis, negative. Phenolsulphonephthalein dye test, total dye excretion of 60 per cent in two hours.

On Feb. 16, 1941, under spinal anesthesia, a vaginal hysterectomy was performed. The postoperative course was uneventful. The patient was discharged from the hospital on Feb. 26, 1941.

From March 10, 1941, to April 22, 1941, she received a total of 30 x-ray treatments. Each treatment was 156 r. without back-scattering. They were given through 4 pelvic portals, 2 anteriorly and 2 posteriorly. The following factors were used: 180 KV, 4MA, 0.5 mm. Cu., 1.0 mm. Al.

Periodic examination revealed no local recurrences, intra-abdominal masses, ascites, or any evidence of metastases. The patient has been symptom free and has not lost weight.

Microscopic examination of the biopsy specimen showed scattered throughout all the sections large areas of edema, inflammation, and necrosis. For the most part the tissue was composed of small, ovoid- to spindle-shaped cells with similarly shaped nuclei. Many of these cells appeared to have cytoplasmic processes, which did not fuse with each other to form a network. This has probably been brought about by the edema, which has dissected the tissue apart. In some areas large cells with eosinophilic cytoplasm were found. The nuclei of these cells were bizarrely shaped and in some instances the cells were multinucleated. They strongly suggested cells of muscle origin. In one field a small area

of necrotic cartilaginous tissue was seen. Mitoses of all elements were numerous. Striated muscle cells could not be demonstrated.

The specimen removed at operation consisted of a soft, club-shaped uterus, 12.5 cm. long. The tubal angles were 5.5 cm. apart and the anteroposterior diameter was 4.5 cm. The external os and cervical canal were widened and coated with iodine. Upon opening the cervical canal anteriorly, an irregularly shaped, soft mass bulged. The lower portion of this mass hung down to within 1.5 cm. of the external os and looked like a blood clot (Fig. 1). The upper portion of the mass was ovoid, with the long axis in the axis of the uterus. The length of the mass, except for the lowermost portion which seemed to consist of a blood clot, was 7 cm.; the transverse diameter was 3 cm. and the anteroposterior

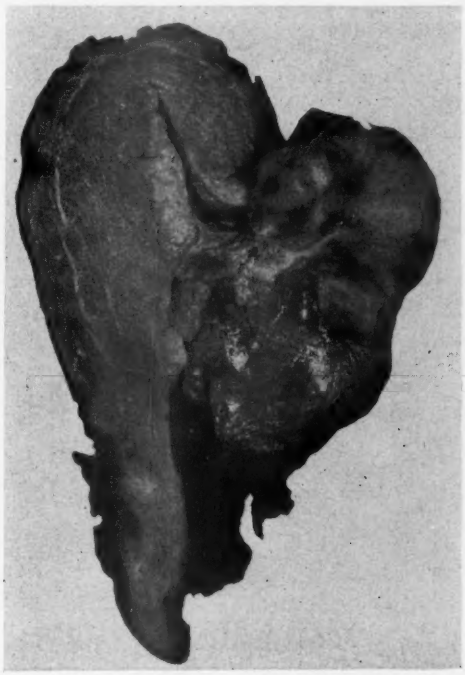

Fig. 1.—Midsagittal section of uterus, after fixation, showing polypoid mass attached to the midportion of the uterine wall by a short pedicle. Above the tumor mass, note the thickness of the endometrium, which was the seat of an adenocarcinoma.

diameter was 4 cm. The mass was soft, highly edematous, partly pale grayish yellow and partly bloody. It was attached to the left side of the uterine wall in its lower half and was also attached to the left half of the posterior uterine wall, including the left tubal angle. Below the attachments, in the region of the external os, there were shallow, yellowish gray protrusions, which seemed to be part of the tumor. A smaller and firmer protrusion was situated in the anterior wall, in the region of the internal os slightly to the right of the midline; to the naked eye this protrusion had no connection with the tumor mass. The endometrium, outside the tumor, was thick, pale, and edematous. It contained a thin-walled cyst, the size of a pea.

Midsagittal section following fixation showed the uterine cavity above the tumor straight, narrow, and appearing to be pushed forward. The

thickness of the submucous muscular layer posteriorly reached 1.7 cm.; the thickness of the entire wall was 3 cm. and that of the endometrium 6 mm. At the upper end of the attachment of the tumor, a thin, gray, slightly curved, membranous layer was seen. This layer appeared to be continuous with the endometrium. The large protrusion on the cut surface was composed of a number of distinctly outlined, grayish masses whose gross appearance was not unlike that of myomas. These masses were separated from each other by narrow and broader bands of partly opaque, but mostly glassy grayish and purplish grayish tissue. The lower part of the tumor was diffusely glassy and yellow. The endometrium above the tumor appeared pale gray and opaque. There was a small area of endometrium-like tissue below the tumor in the region of the internal os. (This corresponded to the swelling described before fixation.) The lowermost portion of the tumor, which appeared bloody from the outside, was also bloody on the cut surface.

Representative blocks of tissue were fixed in formalin and stained with hematoxylin-eosin, van Gieson, Best's glycogen stain, Mayer's mucicarmine, iron-hematoxylin, sudan IV, polychrome methylene blue, and azocarmine.

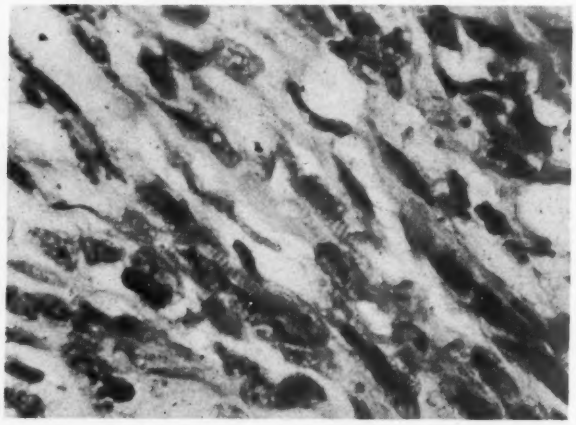

Fig. 2.—Cross-striated muscle cells in a mucoid stroma.

The picture was partly similar to that seen in the biopsy. Necrosis, edema, inflammation, fibrosis, and hemorrhage were unusually extensive in sections taken from the mass which protruded into the uterine cavity. The essential matrix of the tumor consisted of a mucoid tissue containing spindle-shaped or triangular cells with long, fine, protoplasmic strands which appeared to form a network. These areas, however, did not stain red with mucicarmine. In addition a variety of heterologous elements and structures were encountered, both in the tumor mass and uterine wall.

Areas of spindle-cell sarcoma were scattered throughout all sections and were most numerous within the substance of the tumor. In many sections long eosinophilic cells were seen, some of them with longitudinal fibrils. These cells contained centrally placed nuclei, in the vicinity of which definite cross-striations were encountered (Fig. 2). The cells were no wider than the nucleus, but the cytoplasm swelled to accommodate it. Many of the cross-striated cells were short and blunt.

Occasional small islands of cartilage (Fig. 3) were present in sections taken from the tumor. These cartilaginous islands were encircled by a dense collar of small, round cells and spindle cells. Metachromasia could not be demonstrated in such areas when stained with polychrome methylene blue.

Adjacent to some of the areas containing striated embryonal muscle cells were clusters of large vacuolated cells, which somewhat resembled adipose tissue. A negative reaction was obtained when such areas were stained with sudan IV.

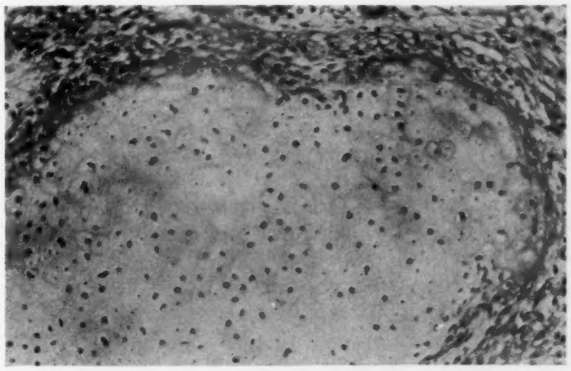

Fig. 3.—Part of an island of embryonal cartilage. An area of spindle-cell sarcoma overlies the cartilaginous tissue.

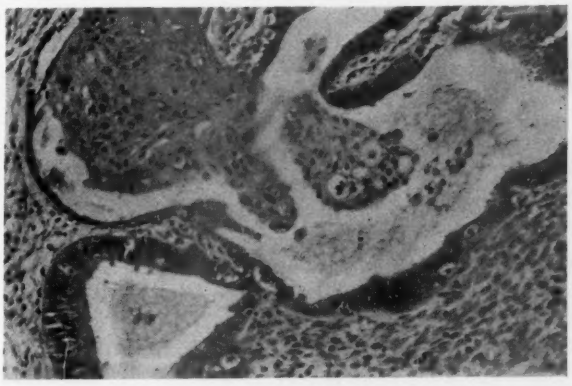

Fig. 4.—An area of adenocarcinoma with squamous metaplasia.

A portion of the endometrium adjacent to the tumor was the seat of the usual type of adenocarcinoma, which in places infiltrated the muscularis for some distance. Areas of adenocarcinoma and sarcoma did not appear to fuse, although the endometrium in some places was seen to be supplanted by sarcomatous areas. Squamous metaplasia was observed in adenocarcinomatous glands (Fig. 4). In some places where the endometrium was not invaded by carcinoma, there was metaplasia to squamous epithelium, which showed keratinization.

A fairly extensive internal adenomyosis was present. In some areas the adenomyotic structures were associated with squamous metaplasia,

and in other areas squamous epithelial plaques were embedded within the uterine musculature, without accompanying endometrial glands.

True lymphatic tissue was not encountered, but sparsely scattered lymphoid foci were seen. Their cells resembled normal adult lymphocytes.

Large, bizarrely shaped, multinucleated cells were occasionally seen in areas containing cross-striated muscle tissue. These cells were not encountered in the endometrium or in areas of apparently uninvolved uterine musculature.

The tumor was richly vascularized with capillaries and thin-walled veins. No tumor thrombi were seen.

DISCUSSION

Histogenesis.—There has been much speculation with regard to the histogenesis of these tumors, and many theories, all unsatisfactory, have been advanced.

The hypothesis, proposed by Pfannenstiel,[15] that the numerous heterologous elements have their origin in the connective tissue of the endometrium and later undergo a process of metaplasia has had little support. A transformation of nonstriated into striated muscle cells has never been demonstrated. Wilms[17] has advanced the theory that the tumors have their origin in primitive mesodermal tissue which has been carried downward during descent of the Wolffian duct. Although the complex nature of the tumor would favor such a concept, the absence of striated muscle in the Wolffian body, together with the development of the tumor outside the course of the Wolffian duct, controvert Wilms' contention.

An origin from cell rests of the Müllerian ducts, following their fusion to form the uterus and upper vagina, seems more plausible, especially since these tumors have been observed to develop at the base of the bladder. Such tumors have never been observed to occur in the broad ligament, and this would contradict the Müllerian duct theory. According to R. Meyer,[12b] embryonal cell rests are not uncommon in the uterus and vagina. These cell rests are epithelial and do not, therefore, lend support to the Müllerian duct theory. This hypothesis has won the support of Mönckeberg,[13] Kehrer,[7] and Lahm.[8]

Differential Diagnosis.—The histologic diagnosis of mesodermal mixed tumors rests upon the demonstration of striated embryonic muscle tissue in combination with one or more heterologous elements like mucoid tissue, cartilage, etc. This has been emphasized by Läwen.[9] The presence of embryonal myoblasts per se does not warrant the diagnosis of mesodermal mixed tumor. A variety of tumors may cause confusion, and in the differential diagnosis, a fibromyoma undergoing ossification or cartilaginous changes, myosarcoma, rhabdomyoma, teratoma, carcinosarcoma, chondroma, myxochondrosarcoma, and the myoblastoma of Abrikossoff[1] must be excluded. If a large number of representative sections are examined and the pathologic criteria of Läwen are followed, there should be no difficulty in diagnosis.

In addition to the variety of elements and structures contained in our case, osteoid tissue[2, 10] and fat[10] have been reported. True bone, bone marrow, lymphatic tissue, and nerve tissue have not been described. A superimposed adenocarcinoma, as occurred in our case, is distinctly uncommon, although carcinomatous changes were present in the cases of Läwen[9] and Nicholson.[14]

Recurrence and Metastases.—Local recurrences have been an almost constant feature in all cases, and distant metastases involving the pleuras, lungs, liver, and pelvic and abdominal peritoneum are frequent. Local extension into the parametria, bladder, and rectum has not been described. Cervical extension is uncommon; it has only been observed in 2 instances.[5, 6] Apparently lymphatic extension does not play a dominant role, as it does in carcinoma of the body of the uterus. Metastases to the lumbar lymph nodes, which are so frequently involved in carcinoma of the body of the uterus, have only been encountered in one case.[10]

Comparison With Cervical and Vaginal Tumors.—The tumors are encountered in the cervix and vagina two or three times more frequently than in the body of the uterus. Vaginal tumors occur during childhood, cervical tumors during the active sexual decades, and corporal tumors during and after the menopause. The cervical and vaginal growths differ from the corporal tumors only in their gross appearance, being arborescent in character. In the body of the uterus the neoplasm is almost always polypoid and frequently is attached to the uterine wall by a distinct pedicle.

Clinical Features.—Symptomatology and physical findings do not differ essentially from the picture presented by carcinoma of the uterus. Since there is no tendency toward infiltration of the parametria and other pelvic viscera, the growth usually remains freely movable, even after it has grown to considerable proportions. It is not unusual for the tumor to attempt to deliver itself through the cervical canal, as occurred in our case and in the cases of von Franqué[3] and Halter.[5]

Panhysterectomy followed by adequate irradiation should be the treatment of choice. There have been no cases on record in which the patients were treated with radiation alone. Inasmuch as the bulk of the tumor is composed of embryonal elements, postoperative irradiation is worthy of a trial.

The prognosis is poor. Recurrence in about one year after operative removal has almost been the rule.

SUMMARY

A case of mesodermal mixed tumor of the body of the uterus plus a superimposed adenocarcinoma has been described. Fourteen similar cases have been collected from the literature. The histogenesis is obscure; the Müllerian duct theory seems the most acceptable, but far from satisfactory. The diagnostic importance of striated embryonic muscle tissue has been emphasized. Total hysterectomy and removal of the tubes and ovaries, followed by adequate irradiation, appears to be the treatment of choice. There have been no five-year cures of verified cases reported.

I wish to thank Dr. Henry C. Falk for permission to publish this case and Dr. Alfred Plaut for his helpful criticisms.

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INTRATESTICULAR HEMORRHAGE: A BIRTH TRAUMA

With a Report of Eight Cases

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THE occurrence of intratesticular hemorrhage during birth in breech presentation is well recognized. It is not generally known, however, that such hemorrhage occurs as a birth trauma when the head is the presenting part. Furthermore, it is not realized that such hemorrhage occurs rather frequently and that it may be quite extensive. An incidental observation of such an instance led me routinely to make gross and microscopic examination of the testicles of newborn infants at necropsy. In slightly over a year, among 21 male infants who died when less than one week old, 7 cases were encountered. An additional one was observed by Dr. Newbill.

REPORT OF CASES

Case 1.—A negro boy was born on Oct. 2, 1940, at 4:32 P.M. of an eclamptic mother at the estimated seventh month of pregnancy. The presentation was vertex and the position L.O.A. The child was blue, responded poorly to resuscitation, and died at 8 A.M. the next day.

At necropsy (A40-1112) the child was 42 cm. long, weighed 1,660 Gm., and had atelectasis of the lungs. There were multiple microscopic hemorrhages in the lungs, liver, kidneys, and in the glomus chorioideum of each lateral ventricle. The testicles were contained in the scrotum and were of usual size. The cut surfaces were dark red. Microscopic examination disclosed massive extravasation of blood beneath the tunica albuginea and in the tissues between the primitive seminiferous tubules (Fig. 1).

Case 2.—A white boy was born on Dec. 13, 1940, at 3:36 A.M. at the estimated ninth month of pregnancy. The duration of labor was about

twelve hours, the presentation was vertex and the position L.O.A. The child was dead at birth.

At necropsy (A40-1349) the child was 44 cm. long, weighed 1,700 Gm., and had fetal atelectasis of the lungs and a "horseshoe" kidney. There were petechiae over the pericardial and pleural surfaces. The scrotum was enlarged and edematous. The testicles were descended and were dark red on their cut surfaces. Microscopic examination disclosed massive extravasation of blood in the tissues between the primitive seminiferous tubules.

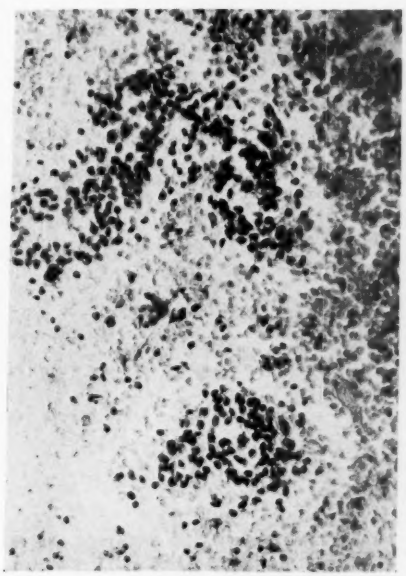

Fig. 1.

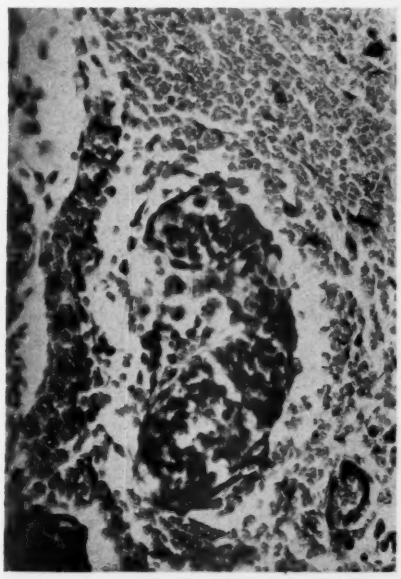

Fig. 2.

Fig. 1.—Massive extravasation of blood between the primitive seminiferous tubules of the testicle of a negro boy who died less than sixteen hours after birth (A40-1112).

Fig. 2.—Extravasation of blood between the primitive seminiferous tubules of the testicle of a white boy who died less than two days after birth (A41-739).

CASE 3.—A negro boy was born on Feb. 18, 1941, at 4:30 A.M. at the estimated seventh month of pregnancy. The presentation was vertex and the position L.O.A. The heart sounds and primary respirations were poor. The child died on February 20 at 1:30 A.M.

At necropsy (A41-198) the child was 39 cm. long, weighed 1,300 Gm., had massive hemorrhage into the lateral cerebral ventricles from the terminal veins, and had atelectasis of the lungs. The scrotum was edematous. Both testicles were descended. The right testicle was proportionate and appeared dark red. Microscopic examination disclosed extensive areas of extravasation of blood beneath the tunica albuginea and hemorrhage into the stroma between the primitive seminiferous tubules, and between the tubules of the epididymis.

CASE 4.—A white boy was born on Aug. 9, 1941, at 8:51 A.M. at the estimated ninth month of pregnancy. The mother was a primipara;

her Wassermann reaction was negative. The duration of labor was about twenty-eight hours; the presentation was vertex; and the position R.O.A. Low forceps was attempted and was followed by spontaneous delivery. The child did not do well and died on August 11 at 6:15 A.M.

At necropsy (A41-739) the child was 50 cm. long, weighed 3,160 Gm., and had bilateral tears in the tentorium cerebelli, fetal atelectasis of the lungs, and uric acid infarcts in the kidneys. There were microscopic hemorrhages in the lungs and glomus choroideum. There was slight edema of the scrotum. The testicles were descended and of usual size. Microscopic examination disclosed focal areas of extravasation of blood in the stroma between the primitive seminiferous tubules, in the hilus, and beneath the tunica albuginea (Fig. 2).

CASE 5.—A negro boy was born on July 31, 1941, at 9:10 A.M. at about term. The duration of labor was sixteen hours, and the position L.O.A. The primary respirations were poor. The child was cyanotic and many petechiae were noted over the body. Vitamin K was given intramuscularly and intravenously, and 10 c.c. of blood were injected into the gluteal region. Each injection was followed by bleeding. The child died at 3 P.M. the same day.

At necropsy (A41-748) (by Dr. Hugh P. Newbill) the child was 52 cm. long, weighed 3,105 Gm., had fetal atelectasis of the lungs with focal pneumonia, and numerous petechiae in the skin, conjunctivae, pleura, and pericardium. There were hemorrhages also in the leptomeninx and dura mater. The testicles were of usual size and dark red on their cut surfaces. Microscopic examination disclosed massive extravasation of blood beneath the tunica albuginea and in the stroma between the primitive seminiferous tubules.

CASE 6.—A white boy was born on Aug. 14, 1941, at 7:10 A.M. at the estimated ninth month of pregnancy. The mother was a primipara. The duration of labor was fifty-six hours. The presentation was vertex and the delivery was with high forceps. The heart sounds were not heard at birth, and there were no primary respirations.

At necropsy (A41-751) the child was 54 cm. long, weighed 4,200 Gm. and had fetal atelectasis of the lungs and microscopic hemorrhages in the glomus chorioideum. The scrotum was edematous, and there was a right hydrocele containing about 3 c.c. of light yellow fluid. The testicles were of usual size and dark red. Microscopic examination disclosed massive extravasation of blood in the septa between the lobules and in the interstitial tissue between the primitive seminiferous tubules and beneath the tunica albuginea (Fig. 3).

CASE 7.—A negro boy was born on Aug. 31, 1941, at 11:55 A.M. at the estimated ninth month of pregnancy. The mother was a primipara, and her Wassermann reaction was positive. The duration of labor was four hours. The presentation was vertex and the position R.O.A. The delivery was spontaneous. The child cried weakly and remained cyanotic. It was placed in an oxygen tent and died at 2:10 P.M.

At necropsy (A41-835) the child was 45 cm. long, weighed 2,330 Gm., had hemorrhage into the right lateral ventricle of the brain from the vena terminalis and had bilateral focal pneumonia. The microscopic

changes in the liver, lungs, spleen, and pancreas were compatible with syphilis. The testicles were symmetrical and dark red. Microscopic examination disclosed diffuse areas of extravasation of blood beneath

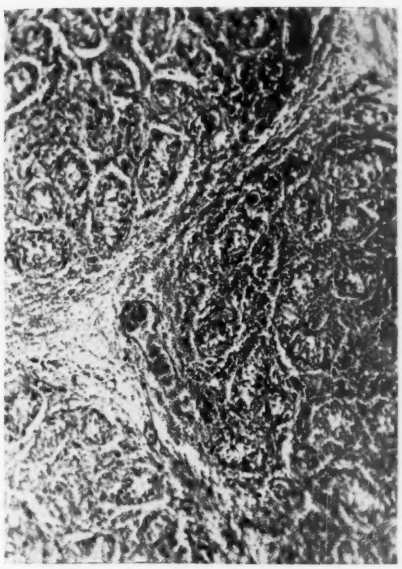

Fig. 3.

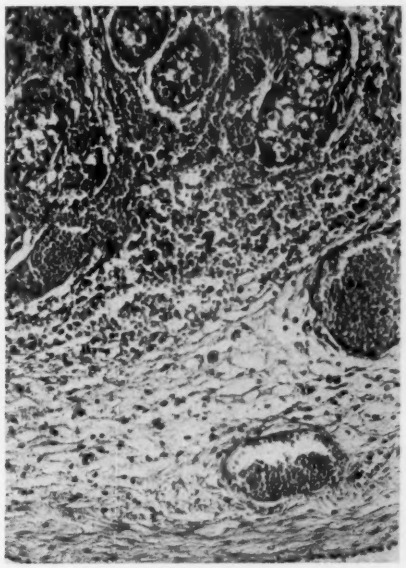

Fig. 4.

Fig. 3.—Extravasation of blood in the septa between the lobules and in the stroma between the primitive seminiferous tubules of the testicle of a white boy who died during delivery (A41-751).

Fig. 4.—Extravasation of blood beneath the tunica albuginea and in the stroma between the primitive seminiferous tubules of a negro boy who died two hours after birth (A41-835).

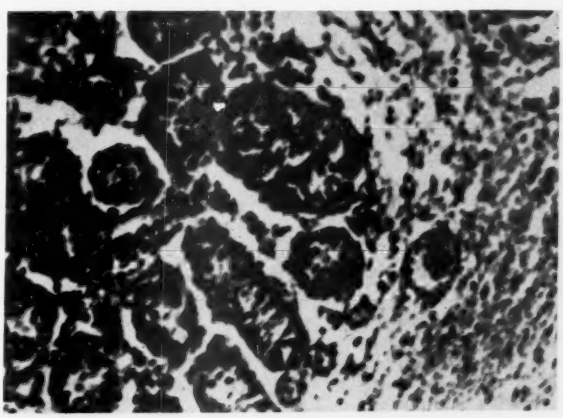

Fig. 5.—Extravasation of blood along the inner surface of the tunica albuginea of the testicle of a negro boy who died less than four days after birth (A41-1032).

the tunica albuginea and in the connective tissue between the primitive seminiferous tubules. Blood-forming islands were seen scattered in the stroma (Fig. 4).

CASE 8.—A negro boy was born in Oct. 23, 1941, at 11:24 A.M. at the estimated ninth month of pregnancy. The duration of labor was fifteen hours, the presentation vertex, and the position L.O.A. The delivery was spontaneous and the child was in good condition at birth. It developed a temperature of 102° F. on October 25 and died on October 27 at 4 A.M.

At necropsy (A41-1032) the child was 50 cm. long, weighed 3,330 Gm. and had suppurative leptomeningitis and bilateral focal pneumonia. Both testicles were dark red, and their capsules were smooth. Microscopic examination of transverse sections of one and of longitudinal sections of the other testis and epididymis disclosed extravasation of blood along the inner surface of the tunica albuginea and in the stroma between the primitive seminiferous tubules (Fig. 5).

COMMENT

In his study on visceral hemorrhages in stillborn children, Spencer[1] (1890) observed intratesticular hemorrhage in 15 of 78 male children. In 8 cases the presentation was breech or footling, and in one case it was vertex, face (?), conduplicatio corpore, and unknown. The 3 remaining cases were described as being delivered by forceps.

Simmonds[2] (1910), in a paper presented before the Biologic Section of the Hamburg Medical Society, was the first to emphasize the frequent occurrence of intratesticular hemorrhage, both in breech presentation and also in head presentation. He regarded asphyxia as the cause of hemorrhage in both instances. In the discussion, Plate explained that after the head had passed through the birth canal the contraction of the vulva forces the blood toward the caudal end of the child. Hemorrhage occurs because the testicles are situated outside the peritoneal cavity, and there is no contrapressure to protect them.

This explanation of Plate perhaps is correct, first because asphyxial hemorrhages elsewhere are not necessarily accompanied by hemorrhage in the testicles, and second because intratesticular hemorrhage may occur in cases in which there is no hemorrhage elsewhere.

SUMMARY

Attention is called to the frequent occurrence of intratesticular hemorrhage as an injury sustained during birth in cases where the head is the presenting part.

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GESTATION FOURTEEN YEARS AFTER RADIUM INDUCED AMENORRHEA*

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THE report of this case is of interest for it presents several problems worthy of consideration because of the widespread use of radiation for various gynecologic conditions.

The possibility of conception occurring following intrauterine radium treatment of pelvic pathologic conditions has been accepted and is an established fact. However, in reviewing the literature on this subject, one finds that gestation after fourteen years' amenorrhea following the intrauterine application of radium is a rare occurrence.

In the treatment of functional female disorders, especially where subsequent pregnancies are desired, the use of radiation has not yet been universally approved. There are many instances reported of the birth of abnormal children following irradiation.[4] It is also noted that there is a tendency toward abortion in the first pregnancies following irradiation, while later pregnancies may terminate in normal offsprings.[1] There is therefore that danger in temporary radium sterilization, and some authorities advocate that permanent rather than temporary sterilization be performed.

Pregnancies have been reported after radium therapy for various pathologic conditions, such as cancer of the body of the uterus, of the cervix, fibroids, *et cetera.*

I. Kaplan[2] reports a case in which carcinoma of the cervix complicating pregnancy was given x-ray therapy and was followed by the birth of a normal child.

C. Karg[1] discusses the history of two women who conceived after restoration of menstruation following intrauterine radiotherapy. Both patients aborted.

P. Burger[3] reviews a series of cases collected by Flaseamp. In 117 patients who had been irradiated with roentgen rays, there were 133 gestations, and among 46 women treated with radium, 54 pregnancies occurred. He states, that it is well known that infants born after irradiation which was given during pregnancy are frequently deformed, the nervous system being particularly involved and defective. In cases where the irradiation was carried out in the pregestational period, the children born after such treatment are nearly always normal. However some authors maintain that such babies may also be born with malformations.

D. P. Murphy[4] reviews over 283 pregnancies in women subjected to pelvic irradiation with the conclusion that "there is yet no definite indication that ovarian irradiation prior to fertilization has any detrimental influence upon the health or development of any subsequent children: that, irradiation of pregnant women is a procedure extremely dangerous to the health of the offspring (61.3 per cent being defective) and should not be undertaken unless the existing pregnancies are to be terminated artificially prior to the period of viability of the child." Of 230 pregnancies occurring in women who received preconception pelvic irradiation, 50 aborted (21.7 per cent). Of the 180 children born at term 27

*Presented at a meeting of the Brooklyn Gynecological Society, December 5, 1941.

(15 per cent) presented some disturbances of health or defect in development.

Ovaries vary greatly in their sensitivity to radium therapy. Most of the full-term deliveries take place within a three-year period after radiation. The less the amount of radiation the more frequent the conception and possible full-term delivery. The chances for conception are least after an 1,800 mg. hours of radiation.

CASE REPORT

Patient S. B., white, 47 years of age, acutely ill and anemic in appearance, was admitted to the Brooklyn Jewish Hospital on May 22, 1941, with a history of backaches for six months and amenorrhea for fourteen years following radium therapy. For the past week patient experienced severe lower abdominal cramps associated with staining and profuse bleeding on the last day. This was accompanied by fainting spells. She had been married for twenty-seven years, and was a para ii, gravida iv, her youngest child being twenty-three years old. Eighteen years previously she was admitted to the Jewish Hospital for an incomplete abortion when a curettage was performed. Fourteen years ago she was treated at the hospital for pernicious vomiting of pregnancy for several days and finally a therapeutic abortion was performed.

Several months later patient was readmitted to the hospital with a history of menorrhagia and metrorrhagia. At this time a dilatation and curettage were performed, and radium inserted for 1,200 mg. hours. The pathologic report of the curettings was that of interstitial endometritis.

Physical Examination.—Head and neck were negative; pupils reacted to light and accommodation; lungs were negative; heart was enlarged, and the sounds were muffled and weak but regular; extremities were negative. The findings at the present admission were: On abdominal examination a mass was palpable, arising from the pelvis and extending halfway to the umbilicus. Pelvic examination revealed profuse vaginal bleeding with blood clots; good parous pelvic floor; a parous cervix which was patulous admitting one finger with which a mass was palpable, suggestive of a submucous fibroid. The uterus was found to be the size of a three months' pregnancy; the fornices were negative. A diagnosis of submucous fibroid was made.

Laboratory Data.—The hemoglobin was 62 per cent; red blood cells, 3.20 million; white blood cells, 10,000; urinalysis, negative; blood pressure, 90/60.

The patient was operated upon on May 22, 1941. A midline infraumbilical incision was made. The uterus was found to be smooth and enlarged to about a three months' gestation. Both ovaries were found to be sclerotic with the right one larger than the left. Both tubes were found to be normal. A supracervical hysterectomy and bilateral salpingo-oophorectomy were performed in the usual manner, the cervical stump being peritonized and hemostasis completed. The abdomen was closed in layers without drainage.

Patient was discharged on the nineteenth day due to a slight wound infection.

Pathologic Report.—Gross Examination: The specimen was a pear-shaped uterus amputated above the cervix with attached tubes and ovaries. Uterus measured 11 by 7 by 4 cm. Its external surface was pink gray, smooth, and glistening. The uterine canal measured 10 cm. in length and was occupied by purple red tissue, clotted blood and a

glistening red membrane. The myometrium measured 1 to 2 cm. in thickness and presented nothing of note. The right Fallopian tube measured 7.5 cm. by 0.4 cm. The fibriated extremity and lumen were patent. The external surface was pink red, smooth, and glistening. The right ovary measured 3.5 by 2 by 1.2 cm. The external surface was pink yellow and gyrated. In the cut surfaces there was a corpus luteum measuring 1.8 cm. in diameter.

The left Fallopian tube measured 6 by 0.4 cm. and was similar to the right.

The left ovary measured 2.5 by 2 by 0.6 cm. and presented nothing of note.

Microscopic Examination: Attached to the endometrial surface was clotted blood in which were seen well-defined chorionic villi lined by preserved Langhans and supercilial cells, as well as poorly defined villi or ghosts of such structure. Syncitial buds were also noted as well as islands of decidual cells. In places there was a dense infiltration by many polymorphonuclear leucocytes. The cellular infiltration was also seen extending into the myometrium. The myometrial bundles were large and spread apart by edematous interstitial connective tissue. Another fragment consisted of extravasated blood with occasional scattered chorionic villi. Two other preparations from the uterus showed similar pictures.

Preparation from the right ovary showed ovarian stroma with a large corpus luteum. The luteum cells were well preserved. The Fallopian tubes showed a narrow lumen, the inner surface of which was thrown into papillary folds covered by cylindrical cells. The connective tissue stalks were delicate. The muscular coat was not remarkable.

Preparations from the left ovary likewise showed ovarian stroma with old and more recent corpora albicantia.

Pathologic diagnosis was a gravid uterus with placental tissue. This was, of course, at variance with our preoperative diagnosis of submucous fibroid, and a postoperative diagnosis of incomplete abortion was made.

CONCLUSION

From the pathologic report of the condition of the ovaries with evidence of follicular activity and recent corpora lutea, we are to deduce that, although no menstruation has occurred, cyclic ovarian function existed. We must, therefore, assume that, due to some change in the hormonal balance, the ovaries had regenerated and become susceptible once more to the constant stimulation of the pituitary gonadotropes. After sufficient regeneration of ovarian function, there is produced an adequate amount of estrogens and progesterone which in conjunction with the activity of some other organs, influence the regeneration and development of the endometrium and uterine activity. This constant stimulation produces a suitable endometrium in time, so that nidation of the ovum and gestation may ensue without the occurrence of any previous cyclic bleeding.

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OVARIAN TUMOR WITH MASCULINIZING SYNDROME

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TRUE masculinizing tumors of the ovary are uncommon and great confusion prevails concerning the pathogenesis, structure, classification, and nomenclature of these neoplasms. Novak[1] classifies those ovarian tumors shown to possess endocrine activity as (1) granulosa cell carcinoma, (2) thecoma, (3) luteoma, (4) arrhenoblastoma, (5) adrenal ovarian tumors, and (6) the so-called struma ovarii or thyroid tumor of the ovary. With the exception of the last two, all are looked on as of dysontogenetic origin arising from abnormalities in the early stages of gonadogenesis.

Reis and Saphir[2] classify true masculinizing tumors as (1) arrhenoblastoma, said to arise from misplaced testicular structures located within or close to the ovary, (2) disgerminoma, believed to arise from early gonad cells before such cells have been differentiated into either ovarian or testicular structure although occasionally disgerminomas do not produce symptoms of masculinization, and (3) hypernephroma, interrenalism or Grawitz tumor, believed by many to arise from misplaced suprarenal cortical rests within the ovary. Others,[3] however, believe that these tumors arise from lutein cells of the ovary and therefore designate them as luteomas.

The evidence presented herewith seems to indicate that the following case falls within this latter category.

REPORT OF CASE

Miss B. V., an unmarried girl of Spanish parentage, aged 23 years, came under observation on Nov. 29, 1938. Except for pneumonia in infancy, her past medical history was unimportant. Family history revealed that her mother died of cancer of the stomach at the age of 30, and her father died of tuberculosis at the age of 30. Her menses began at 14 years and were regular until 1935 when amenorrhea occurred for one year, followed by irregularity. With the onset of amenorrhea there was a coincidental overgrowth of hair, at first on the face and chest, later covering the back, abdomen, and legs. She gained 30 pounds following the beginning of her illness but lost 10 pounds during the past six months. During the past five months she complained of menorrhagia and metrorrhagia.

Physical Examination.—The patient was a short (61 inches) and somewhat obese young woman weighing 131 pounds. The obesity involved the trunk, neck, and face, being much less marked in the extremities. The texture of the skin was coarse, and there were numerous purplish-brown striae along the sides of the abdomen, the hips, and the breasts. Her voice was husky but still feminine. There was pronounced hypertrichosis of the entire body, the hair being heavy, black, coarse, and of definite male distribution with pudendal excess extending above the umbilicus (Fig. 1). Hair had been removed from the face by x-ray treatments given elsewhere six months prior to admission to

the Clinic. The arms and legs were heavily covered as were the dorsal surfaces of the fingers and toes. The eyes were prominent and the face moon shaped.

Vaginal examination showed marked hypertrophy of the clitoris which measured 1 cm. in diameter and 1½ cm. in length. There was a purulent bloody discharge from the vagina. The cervix was firm and irregular, and a small, fatty mass protruded from the external os. The uterus was markedly enlarged and measured about 10 by 14 cm. in diameter. It was hard, smooth, and movable. The adnexa were not palpable.

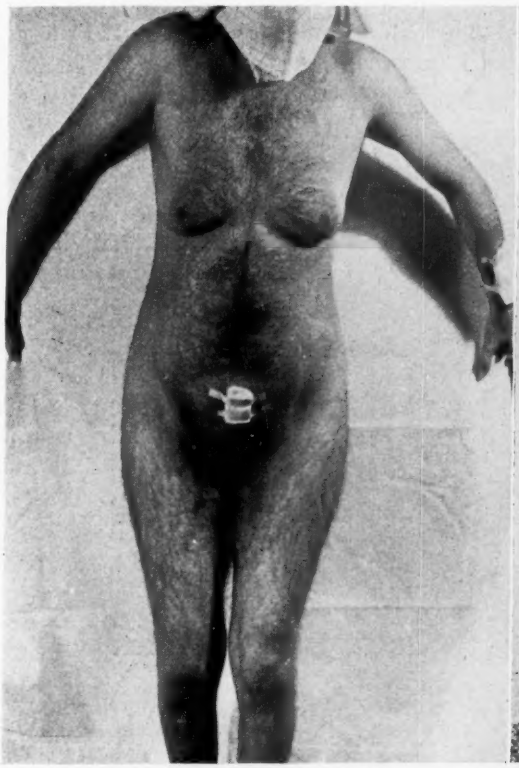

Fig. 1.

Fig. 2.

Fig. 1.—Prior to removal of the ovarian tumor.
Fig. 2.—One year after removal of the ovarian tumor.

Roentgen examination of the skull, sella turcica and long bones showed no unusual changes other than a slight amount of decalcification of the dorsum sellae.

Laboratory Data.—The urine was negative except for a few pus cells in clumps. The blood count showed 11,500 leucocytes, 4,600,000 erythrocytes, and 71 per cent hemoglobin. The blood Wassermann was negative. Chemical analysis of the blood showed 200 mg. of cholesterol, 10.4 mg. of calcium, 320 mg. of sodium, and 511 mg. of sodium chlorides per 100 c.c. The carbon dioxide content was 56 volume per cent. The dextrose tolerance test showed 91 mg. of sugar per 100 c.c. during fasting, 250

mg. one-half hour after ingestion of 100 Gm. of dextrose, 246 mg. after one hour, and 200 mg. after two hours.

At operation on Feb. 3, 1939, the uterus was found to be symmetrically enlarged to the approximate size of a three months' pregnancy, and contained a small nodule on the anterior aspect. The right ovary was smaller than normal and appeared sclerotic. The left ovary was enlarged to the size of 4 to 5 cm. in its widest diameter. The left ovary and uterus were removed after careful palpation of both renal and adrenal regions had failed to demonstrate any adrenal tumor.

The postoperative course in general was very stormy. Immediately following operation the patient was in a state of surgical shock. Large amounts of adrenal-cortin, together with other measures taken to combat shock, brought about a notable improvement within forty-eight hours. The patient remained in the hospital for three months during which

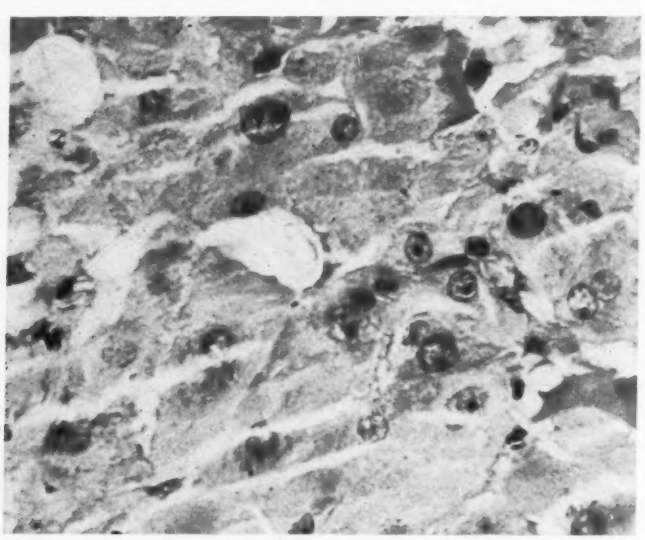

Fig. 3.—Photomicrograph (high power) showing section of the ovarian tumor. Hematoxylin and eosin stain. Note large polyhedral cells, clear cytoplasm, and distinct cellular outlines.

time she frequently manifested emotional and nervous upsets, such as persistent emesis, headaches, and spells of crying. Furuncles appeared frequently in various areas and the surgical wound was slow in healing. After four months, her emotional adjustment and general health were near normal. The hirsutism on the chest and back had markedly decreased, the voice was softer but the size of the clitoris had not diminished. A year later (Fig. 2) the breasts were larger, the figure had become more feminine and the masculine distribution of hair had entirely disappeared. The clitoris had decreased in size.

*Pathologic Report.**—The specimen consisted of an ovary and uterus. The ovary measured 6.5 cm. in diameter, was semifluctuant in consistency, and had a bluish green capsule. Approximately two-thirds of the ovary was composed of a single cyst measuring 4 cm. in diameter and lined by a smooth grayish pink surface. It contained turbid, reddish

*The author is indebted to Dr. Angus Wright and Dr. A. R. Camero for their assistance and advice on the pathologic aspects of this case.

brown, thin fluid. The adjacent portion of the ovary was composed of a firm rim of brownish yellow, cellular tissue, apparently enclosed within the capsule of the ovary. The uterus measured 14 by 9 by 9 cm. in diameter and had a small fibromatous nodule beneath the serosa. The cut surface showed thin, cordlike whorls of fibrous connective tissue within the myometrium.

Histologic examination of the ovary showed that the brownish yellow tissue described before was grossly made up of large cells containing an abundant amount of granular, pink-staining cytoplasm (Fig. 3) with large nuclei and conspicuous nucleoli (Fig. 4). These cells were arranged in irregular strands and many of them contained granular brown pigment within their cytoplasm and some of them exceedingly large nuclei. A number of large spaces within the tumor were lined by cells of the type described. Fat stain showed that the large cells

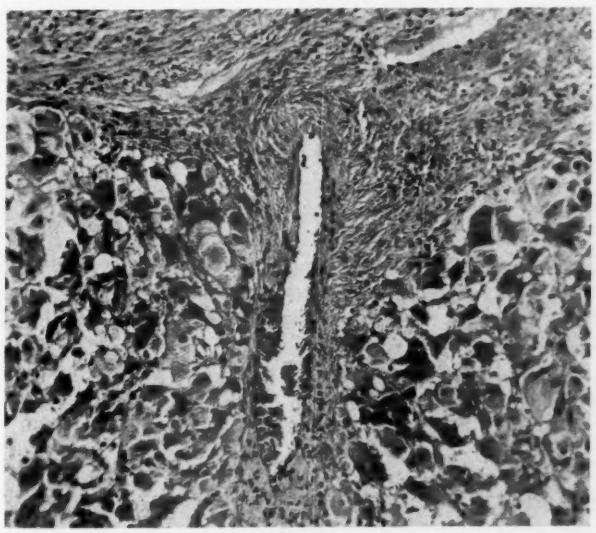

Fig. 4.—Photomicrograph (low power) showing section of the ovarian tumor stained with hematoxylin and eosin. Note the large, polyhedral cells, abundant cytoplasm with large nuclei and conspicuous nucleoli.

contained a few fine granules of fat-staining material in addition to brown pigment which did not stain. Ponceau-Fuchsin stain showed that these cells gave the reaction of virilism as noted in certain cortical adrenal tumors.

DISCUSSION

Kermauner believes that such tumors arise from lutein cells of the ovary. Masson[4] points out that the luteoma may be recognized by a fine, reticulum network similar to that seen in the corpus luteum and that such reticulum cannot be found in tumors which arise from the suprarenal cortex, but Saphir[5] counters with the statement that there are hypernephromas in which reticulum is demonstrable. Novak[6] expresses doubt that the mature functioning lutein cells could be the source of tumor growth. He believes that certain granulosa cell cancers can exhibit a lutein-cell transformation of the constituent cells to such an extent that the tumor might be converted into a lutein-cell tumor. He

and Plate[7] have individually seen such histologic transformations in parts of tumors which were clearly of the granulosa-cell variety. Schiller[8] coincides with Novak and is convinced that, with a very few possible exceptions, such tumors are of the adrenal rather than the lutein character. On the other hand, Reis and Saphir are convinced that, anatomically, it is not possible to differentiate between lutein cell blastoma and hypernephroma but that both types of tumor may coexist or develop in the ovary. Hochloff[9] called his tumor a hypernephroma of the ovary but Kermauner believed that the tumor might equally have been called a lutein cell blastoma.

When Rottino and McGrath[10] submitted slides of their case to various physicians, E. Novak, R. Meyer, W. Schiller, and D. Symmers expressed the opinion that the growth arose from an adrenal rest. Vines and Broster,[11] however, felt that the growth was not of adrenal origin and suggested luteinic origin instead. Saphir, who also studied a slide, believed that it was a true tumor-luteoma or hypernephroid and different from his case. Rottino and McGrath concluded that, aside from size, they could see no difference between their case and that of Saphir's.

Norris[12] is convinced that positive identification of these tumors cannot be made until the hormone is isolated and its physiologic activity demonstrated. He recommends that hormonal studies be made before and after operation to help establish the nature of the disturbance. Schiller points out, however, that the ovaries develop substances of virilizing effect and that testicles produce folliculin. What holds for the physiologic tissue may be found in even greater degree in tumors developing from it. For that reason, he thinks it is not safe to prove the origin of virilizing or masculinizing tumors by their production of substances of sex influencing capacity. He believes that, for the time being, it is much safer to rely on morphologic criteria exclusively for the classification of such tumors.

SUMMARY

The case presented here may be regarded as an instance of the condition under discussion, for clinical masculinity developed in a patient who previously had been completely feminine. Furthermore, the removal of the left ovary was followed by a reversal of symptoms with re-establishment of female habitus. The yellowish-brown tumor of the left ovary was composed histologically of large, clear, fat-containing cells with large nuclei arranged in irregular strands. The resemblance of these cells to corpus luteum cells was most conspicuous, and it seems logical that this tumor and the clinical picture can best be explained as a result of tumor development with a perversion of secretion of the lutein cells.

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A FRATERNAL TWIN PREGNANCY

Observations on the Maternal Ovaries and on the Twins in Utero

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THAT twins of the fraternal variety originate in the fertilization of two ova is unquestioned, but whether these ova are liberated both from one ovary, or from two follicles or one, obviously can be determined only in exceptional instances. The infrequency of twins[1, 2] is an initial handicap in the collection of such data. The difficulties are increased by the extreme rarity of opportunities to combine in the one case all the observations which are necessary for full interpretation, including the ovaries in the twin gravid woman, the twins and their membranes. In the instance here reported, it can be stated definitely that the twins are fraternal, for they are opposite sexed and dichorionic. The corpora lutea furnish evidence of their origin from ova liberated from separate follicles of the same ovary. Significantly, the corpora are so closely approximated that on superficial examination of the ovary they would have appeared as one mass.

DESCRIPTION

No history of the case is available, the specimen having been recovered without an identification mark among materials which had been long in storage in a hospital laboratory. The specimen comprises the uterus and adnexa, with a twin pregnancy advanced to about the beginning of the eighth lunar month.

The anterior wall of the body of the uterus had been slit lengthwise over a distance of some 15 cm., evidently only to admit the preservative or for a casual inspection of the interior. The uterine contents had not been disturbed except for incision of the membranes at this opening. The original slit being of too narrow a gape for the desired preliminary examinations, the exposure was increased by excising strips laterally and toward the extremities of the uterus, but with care to preserve the original relations of the membranes and fetuses. The drawing reproduced in Fig. 1, based mainly on photographs of the specimen made at this point, leaves little for description.

The total length of the fundus and corpus uteri is 25 cm. The maximum transverse diameter is 20 cm., while the maximum anteroposterior dimension is about 15 cm. These measurements obviously fall short of representing the size of the uterus before the release of amniotic fluid.

There is a single oval placenta, measuring 13 by 18 cm., the greater dimension being aligned with the long axis of the uterus. It lies on the posterior wall, and is centered slightly to the left of the midline. The umbilical cords are attached in the central area of the placenta, the cord insertion of the male fetus being 6 cm. directly superior to that of the female. Each fetus is enveloped by its separate amnion and chorion. The septum between the amniotic cavities is readily split into four layers: amnion, chorion, chorion, amnion.

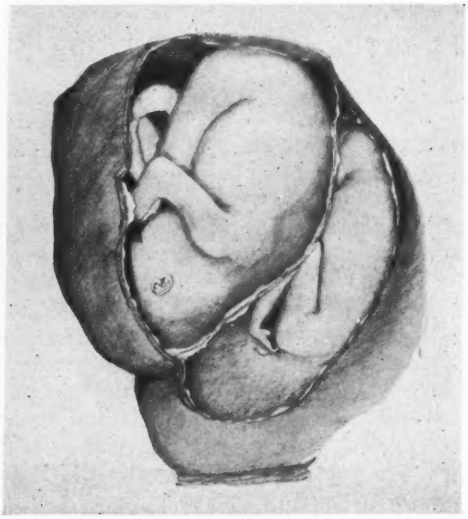

Fig. 1.—The uterus, opened anteriorly, showing the two fetuses (the male lying superiorly and more fully exposed) with their membranes. The placenta, attached to the posterior wall, is entirely covered.

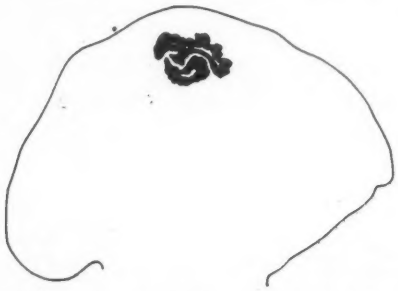

Fig. 2.—Tracing from a section of the right ovary, showing the close approximation of the two corpora lutea.

The crown-rump length of the male fetus is 21 cm., that of the female, 20 cm. The measurements point to a menstrual age of six lunar months, but the external differentiation of the fetuses (especially in hair development, disjunction of eyelids, growth of lashes, and length of nails) indicates that they are in or very near the eighth lunar month. The fact that they are twins may account for the failure to attain body sizes equal to the average of fetuses, in single pregnancies, which present equivalent advance in differentiation.

After examination, both ovaries were cut serially in celloidin, sections at close intervals being then selected and stained with hematoxylin and eosin for permanent mounting. The sections revealed no evidence of a corpus luteum in the left ovary, while the right one presented the "twin" corpora shown in Fig. 2. In maximum breadth and length this right ovary measured 30 by 42 mm., with a maximum thickness of about 10 mm. When its surface was inspected no evidence of the corpora was detectable, perhaps because of their depth as well as fading due to prolonged preservation. It is clear from the relationship of the two corpora that the follicles likewise must have been closely appressed, perhaps in a relation so intimate at the time of rupture as to produce a single massive elevation.

DISCUSSION

The occurrence of two types of twins is generally accepted: "identical," of single-ovum origin; and "fraternal," arising as in the present instance from two ova. Various suggestions have been advanced[3, 4] in regard to the possible existence of a third type, produced by separate fertilizations of an ovum and polar body or by bispermy in a binucleate ovum, as well as classes of "identical" twins differing in embryogenesis. The twins under consideration are definitely not "identical," being unlike-sexed.

We may proceed to the ovarian evidences which call for attention in the interpretation of twin cases, considering first the number of corpora lutea. Two corpora may be frankly evident, as in the case reported by Essen-Möller,[5] who, in performing supravaginal amputation of the uterus in early pregnancy, noted a large corpus luteum in each ovary; when the uterus was later opened, it was found to contain two embryos, their separate chorions being in keeping with the conclusion of biovular origin. In the work of Allen,[6] on recovery of human ova from the uterine tubes, there is reported an example of double ovulation offering an exact parallel. An ovum was recovered from each tube, and a corpus luteum was present in each ovary; the ova thus may be regarded as having been the potential source of fraternal twins, both ovaries participating as in Essen-Möller's case. Other cases are on record, both for double ovulations and actual twin pregnancies, in which only one ovary is concerned.

Stein[7] voices a caution respecting instances in which apparently only one corpus luteum is present, pointing out that a second inconspicuous corpus may be overlooked. His remark doubtless applies particularly to the inspection of ovaries at operation. Its aptness is borne out by the findings in the ovary here described. Stein's warning should be extended to cases where two corpora are observed, since a third one might pass unnoticed in the same manner.

The factor of embryonic mortality[8] is of sufficient importance to call for attention in deductions based upon the number of corpora lutea. In this case, for example, it might be postulated that the twins originated from two ova developed in one follicle, and that if the ovum released from the other were fertilized the embryo had died and was absorbed. Such an interpretation does not call for serious consideration in the present instance, in view of the fact that a careful search of the sections of both ovaries did not disclose a single follicle containing more than one

oocyte (polyovular follicles being characteristically fairly numerous when they occur at all).

With assurance that a single corpus luteum is present, the associated twins may be of either the "identical" or fraternal variety. Wieman and Weichert[9] report on a specimen obtained at autopsy, the uterus containing same-sexed dichorionic twins and the ovaries presenting but one corpus luteum. The authors conclude that a bi-ovular follicle had produced the ova, giving rise to these twins. The occurrence of such follicles in the human ovary is well established.[10] The question then arises as to whether it is justified to relate the individuals, in cases of fraternal twins such as the one here reported, to separate follicles corresponding to the two corpora lutea. In the present case the conclusion seems to be reasonably sound; as pointed out, neither ovary contains polyovular follicles.

SUMMARY

The intrauterine relations of a pair of fraternal twins (male-female; dichorionic) near or in the eighth lunar month are described. The maternal ovaries, prepared histologically, show that the twins arose from ova in separate follicles of the right ovary, as indicated by the presence in it of two corpora lutea and the absence of a corpus in the left ovary. Since the two corpora lutea are very closely approximated it is quite probable that surface inspection of the ovary would have failed to disclose the double nature of the mass. Inspection of the ovarian surface at laparotomy is the only feasible observation in some twin cases, and the present finding points a warning against assuming that the full number of corpora lutea is invariably noted by this means.

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To the heretofore reported approximately 200 cases of round ligament tumors, the authors add five new observations. They were an endometrioma, a fibroma, two cystic tumors (a congenital multilocular cyst and a cystic hygroma), and a capillary hemangioma with areas suggestive of benign angioendothelioma. The latter condition seemingly has never before been recorded in literature. The two cystic tumors were associated with indirect inguinal hernias.

The most common type of round ligament tumors are fibromas, followed by endotheliomas in regard to frequency.

HUGO EHRENFEST.

BILATERAL DERMOID CYSTS COMPLICATING PREGNANCY*

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THIS case is presented not only for its scientific interest, but also because of the multiplicity of complications in a patient twelve weeks' pregnant.

H. K., white, 33 years of age, gravida vi, para i, was admitted to St. Mary's Hospital, Brooklyn, N. Y., April 1, 1941, complaining of pain in the left lower abdomen and of vaginal bleeding.

The last menstrual period began Dec. 24, 1940. It was normal in character and lasted the usual three days. The patient was well until Jan. 22, 1941, on which date she began to have spotty vaginal bleeding. This spotting was present daily until Feb. 20, 1941. She was then free of bleeding for about one month, but from March 17, 1941, up to the time of admission to the hospital there was daily recurrence of the spotting.

One week prior to entrance into the hospital the patient was seized with severe, cramplike pain in the left lower quadrant of the abdomen, and she felt as if she were going to faint. Although the pain diminished in severity, a residual soreness continued in the left lower abdomen.

Abdominal examination revealed extreme tenderness, with some tenseness, in the left lower quadrant. A tender mass could be palpated about two and one-half fingerbreadths above the symphysis.

Vaginal examination disclosed a soft uterus which was approximately three times normal size, with an extremely tender mass filling the posterior cul-de-sac. A larger, cystic mass was palpated in the left lower quadrant which was movable and tender.

A provisional diagnosis of an unruptured ectopic pregnancy with a left ovarian cyst was made and laparotomy advised. The blood count showed 4,150,000 red blood cells, 85 per cent hemoglobin, neutrophiles 60 per cent, and lymphocytes 38 per cent. The urine was negative. Laparotomy on April 4, 1941, revealed the following: (1) Right dermoid cyst the size of a large orange, filling the posterior cul-de-sac. (2) Left dermoid cyst the size of a grapefruit, with a twisted pedicle, rising above the pelvis and situated in the left lower quadrant of the abdomen. (3) An intrauterine gestation of three months' duration.

A bilateral total oophorectomy was easily performed under basal avertin anesthesia, supplemented by nitrous oxide, oxygen, and ether.

The postoperative care included: (1) Morphine sulfate, gr. ⅙, every four hours for two days. (2) Progesterone, 5 mg., t.i.d., from April 4 to 7, 1941 (three days). Progesterone, 5 mg., b.i.d., from April 7 to 12, 1941 (five days). Progesterone, 5 mg., u.i.d., from April 12 to 16, 1941 (four days). (3) Progesterone, 5 mg., once a week until May 9, 1941 (one month). (4) Wheat germ oil, 2 dr., t.i.d., from April 12 to 16, 1941.

The postoperative course was entirely uneventful and there was no morbidity. The patient was discharged from the hospital May 16, 1941.

*Presented at a meeting of the Brooklyn Gynecological Society, December 5, 1941.

Follow-up visits in the clinic revealed that pregnancy was progressing satisfactorily. The patient was delivered of a full-term living female child, Sept. 27, 1941, by low prophylactic forceps, 176 days after operation. Lactation of the newborn was normal.

Pathologic Report.—The specimen consisted of two cysts, one about the size of an orange; the other, somewhat elongated, was larger, about the size of a grapefruit. Both cyst cavities were surrounded by a thickened, almost transparent capsule. They were filled with a large amount of yellowish, caseous, cheeselike material in which were found numerous clumps of thickened, brown to yellowish, hair. Both cysts resembled dermoid cysts in type.

Microscopic sections showed a fibrous cyst wall which, in some places, was outlined with several layers of cuboidal epithelium. There were a few remnants of atrophic sebaceous glands present. Both cysts were similar in structure.

DISCUSSION

Dermoid cysts account for 10 per cent of the cystic neoplasms of the ovary (Novak[1]), 25 per cent being bilateral. Dermoids are benign cystic ovarian tumors characterized by a predominance of ectodermal elements containing sebaceous material, hair and other forms of ectoderm and occasionally some mesodermal elements.

Bilateral ovarian dermoids complicating pregnancy, in which bilateral ovariotomy is performed, are of especial interest because of their rare incidence. The available literature reveals only 46 reported cases. Andrews and Nicholls,[2] in an exhaustive review of the literature, found 43 cases and report a case of their own. King[3] and Southward, Jr.,[4] have each reported one case. Thirteen patients, not including the case reported herein, were operated upon within the third month of pregnancy. The successful conclusion of pregnancy in 11 of these (two having aborted) initiates an interesting endocrinologic discussion.

Experimental evidence, as shown by the literature, reveals the belief that the placenta completely assumes the hormonal functions of the ovary. Not only has progestin been found in the placenta, but estrogen fractions have also been recovered. Smith and Smith[5] and their coworkers have presented exhaustive studies of hormone assays in both the normal and abnormal types of pregnancies, including the toxemias. These hormonal reports evaluate in detail the total amounts of chorionic-gonadotropin, estrogen and progestin excreted daily during pregnancy. It is interesting to note at this point the tremendous advantage that the combination of research worker and clinician has over the purely scientific or clinical investigator, because he has at hand the statistical findings to support his clinical observations.

Seegar and Delfs,[6] in a study of pregnanediol excretion following bilateral oophorectomy in early pregnancy, report cases "in which the corpus luteum of pregnancy was removed on the one hundred and twentieth and fifty-fourth days, respectively, and pregnanediol excretion subsequently remained within normal limits. These cases seem to lend additional support to the theory of a placental origin for progesterone during pregnancy. However, in both cases functional ovarian tissue remained." They also report a case of their own in which pregnancy continued normally after removal of all ovarian tissue on the fifty-sixth day of gestation. Serum gonadotropin and pregnanediol assays were done in this particular case. The former was found to be within normal limits as compared to normal pregnancy. The pregnanediol assays, how-

ever, were lower than normal, varying from 3.5 mg. per twenty-four hours in early gestation, to 20 mg. at the ninth month, instead of from 5 to 100 mg.

Supported further by the successful conclusion of pregnancy in the 11 reported cases (12 including our own) in which bilateral oophorectomy was performed within the third month, it is our contention that the placenta, once it has been well established, plays the all important role of custodian of gestation, superseding the corpus luteum. The exact period at which this transfer takes place has not as yet been definitely established. Jones and Weil[7] report that progestin production begins to take place about the sixtieth day of pregnancy. It is safe to assume that total transfer of function with complete safety to the fetus is assured at least by the ninetieth day following conception. With this in mind, the value of progestin therapy in our case is problematic. However, used as a complement to the already existing hormones, progestin probably acted as a sedative to the uterus. The important role of progestin in lessening uterine sensitivity and contractility has already been established by Lubin, Reynolds and Clarke[8] in post-partum afterpains and by numerous others in threatened abortion. It probably also bridges the gap of diminished hormonal production following the trauma of an operative procedure. The synergistic action of estrogen and progestin, as brought out by Smith and Smith in 1940, would have warranted a trial of therapy. That is to say, that the therapeutic action of progestin would have been enhanced by the simultaneous use of estrogenic hormone.

CONCLUSIONS

1. Another instance of pregnancy complicated by bilateral dermoid cyst, followed by bilateral oophorectomy, has been added to the 46 cases already reported in the literature.

2. An attempt has been made to enhance the established belief and advance it to the stage of factual conclusion that the placenta takes over the complete role of the ovary at about the third month of gestation.

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FIBROMA OF THE OVARY ASSOCIATED WITH ASCITES AND HYDROTHORAX (MEIGS' SYNDROME)*

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IN 1937, Meigs and Cass[1] called attention to the clinical entity of fibroma of the ovary accompanied by a serous transudate in the abdominal and in one or both pleural cavities. They reviewed the seven cases that had been reported in the past twenty-five years and shortly thereafter added eight others.[2] They were not the first to record this syndrome, since Owen[3] and Hoon,[4] in 1923, described the association of an ovarian fibroma with hydrothorax and ascites. Meigs and Cass,[1] however, emphasized that such cases could be cured by removing the ovarian tumor in spite of the grave appearance of the patient.

Ovarian fibromas comprise 1 to 4 per cent of all ovarian tumors. A fair average would appear to be 2 per cent.[8] Ascites alone is a frequent finding in such tumors. Only 18 cases have been reported in the literature of ascites and hydrothorax occurring with these neoplasms, in which the fluid disappeared spontaneously following removal of the mass. It is fair to presuppose that many more cases have undoubtedly occurred but have not been reported.

In the recorded cases of Meigs' syndrome, the patients' ages varied from thirty-one to sixty-four, though the majority were at or near the menopause. As a rule, the chief complaint was dyspnea or a dragging sensation in the lower abdomen with the knowledge of a mass in that region for varying periods of time. In one case, the mass was known to have existed for eight years. Occasionally, abdominal paracentesis was necessary before the tumor could be felt. Cachexia was common, due to rapid dehydration. The correct diagnosis was usually difficult to make, since the condition closely resembles pelvic malignancy.

There were two deaths in the 18 reported cases. The actual cause of death was difficult to determine. One patient was never operated upon, while in the other, the fibroma was complicated by pregnancy with eclampsia. In both instances, it was apparent that delaying the operation contributed to a more rapid demise.

Bomze and Kirschbaum[5] pointed out that many of these patients were hospitalized for symptoms suggestive of heart failure. In addition, several had electrocardiographic findings substantiating the diagnosis of heart disease. These men suggested that the fluid might be caused by the added strain upon the heart due to pressure by the heavy tumor in one who is just within the bounds of compensation; or it might be due to an interference in the pelvic and lower abdominal circulations. Significantly, the fluid rapidly re-accumulates following thoracentesis or paracentesis but spontaneously disappears following surgical removal of the tumor. In one case, 5 thoracenteses were done in four weeks with a

*Read at a meeting of the Brooklyn Gynecological Society, December 5, 1941.

total of 8,900 c.c. of fluid removed.[9] The decompensation theory does not adequately explain the presence of the transudate, yet, we have no better one to offer.

The fluid has been found sterile despite many attempts to isolate organisms by cultural or animal inoculation methods. Malignant cells have never been demonstrated. The physical and chemical characteristics are those of a transudate. Blood studies, especially serum proteins, are within normal limits.

The fluid is more frequently found in the right pleural cavity though it has been noted in the left pleural sac on several occasions and in one case was bilateral. The location of the fluid bears no relationship to the position of the tumor although the right ovary is most frequently involved. In 3 cases, both ovaries were the seat of fibromas.

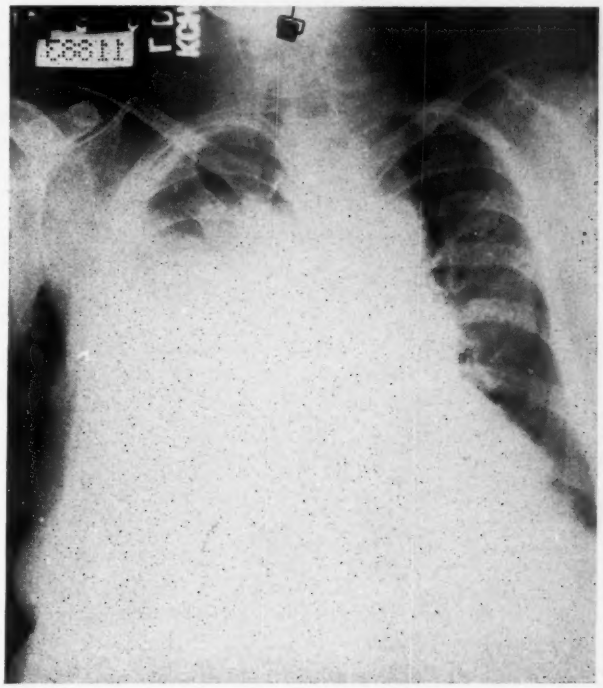

Fig. 1.—On admission, x-ray revealed a pleural effusion on the right side extending to the sixth rib in the axillary line.

Pathologic examination of the neoplasm revealed it to be an encapsulated cellular fibroma. Areas of cystic degeneration and necrosis are common. Following removal of the tumor, recurrences have not been reported though cases have been followed for as long as twenty-seven years.

Such a case was recently observed at the Kings County Hospital and is being reported because it represents this syndrome occurring in the oldest patient on record.

CASE REPORT

Mrs. A. M., a 73-year-old, white woman, was admitted to the Medical Service of the Long Island College Division of the Kings County Hospital on March 4, 1941. For the past three months she had complained

of shortness of breath and swelling of the abdomen. Her troubles started in November, 1940, when she experienced increasing dyspnea on exertion and noted that her abdomen was becoming larger. Two years ago, she had been hospitalized for "an episode of decompensation" similar in all respects to her present difficulties. The menopause had occurred at the age of 48, and there had been no bleeding or discharge since.

On admission, the temperature was 99.8° F., pulse 75, respirations 20, and blood pressure 158/85. She was dyspneic, orthopneic, and markedly cyanotic. Physical examination revealed the following significant findings: dullness over the entire right upper chest down to the third rib with flatness from this level to the base, anteriorly and posteriorly. No

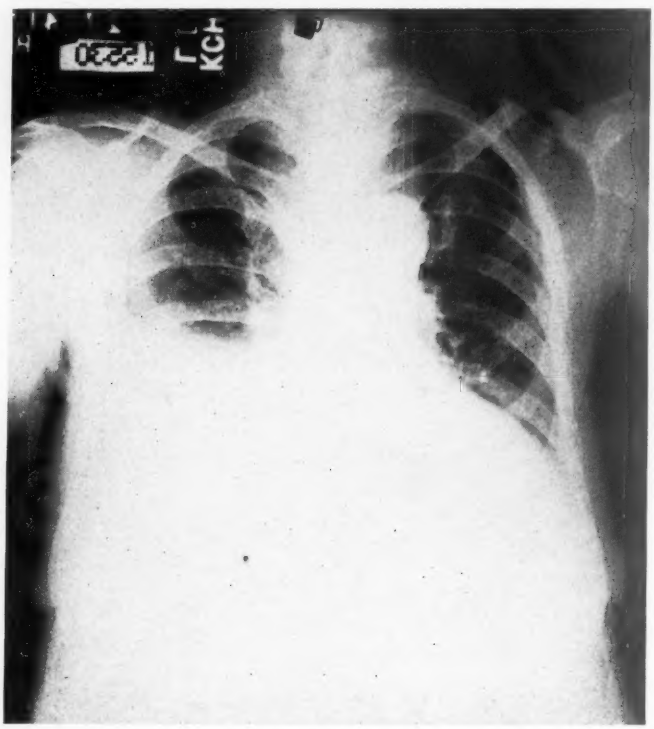

Fig. 2.—X-ray taken before operation and after thoracentesis showed fluid in the right side extending to the seventh rib in the axillary line.

breath sounds were audible over the right chest though the left side was clear. A soft systolic murmur was heard at the apex and the heart was slightly enlarged to the left. The abdomen was markedly distended, the percussion note flat, and a fluid wave with shifting dullness was present. Both feet, ankles, and legs up to the knees were markedly edematous.

The urine was negative. The white cells numbered 18,500 with 68 per cent polymorphonuclear leucocytes. The red cells numbered 5.25 million and the hemoglobin was 78 per cent. The blood urea was 27 mg. per cent and the blood Wassermann was negative. The electrocardiogram was reported as showing extensive myocardial fibrosis. Roentgenogram of the chest (Fig. 1) revealed a pleural effusion on the right extending to the sixth rib in the axillary line with elongation and calcification of the aorta and preponderance of the left ventricular contour of the heart.

The medical staff was of the opinion that the patient was suffering from decompensation due to hypertensive cardiovascular disease. She was given mercurial diuretics and digitalized. Moderate diuresis was established, and by March 8, the peripheral edema had almost completely disappeared. The abdominal fluid decreased sufficiently to permit the palpation of a large mass. Some fluid was removed from the chest for diagnostic purposes and revealed many red cells though no lymphocytes or malignant cells were seen. A gynecologic consultant, on March 25, described the mass as being eight inches in diameter, firm in consistency, freely movable, slightly nodular, insensitive and originating from the pelvis. Its upper limit extended slightly above the umbilicus. The

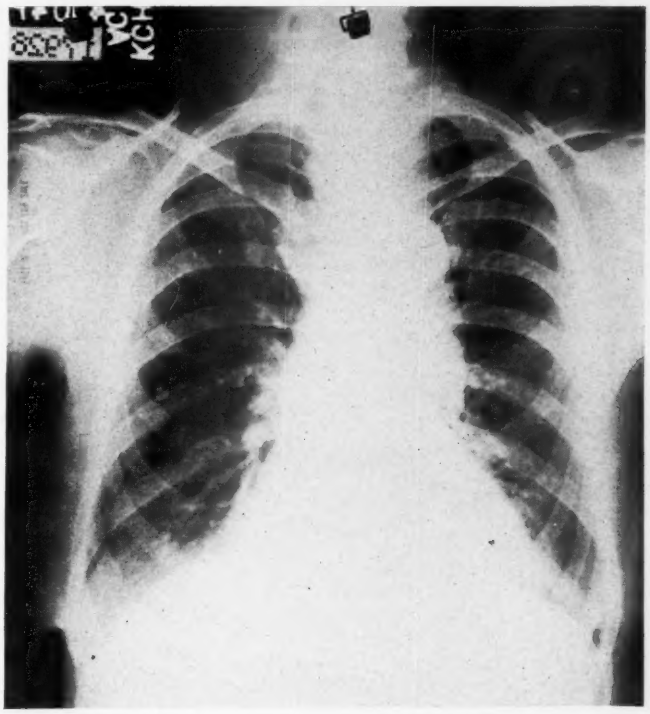

Fig. 3.—On the sixth day postoperatively there was no fluid in the right pleural sac.

pelvic examination disclosed a senile vaginitis with the cervix flush with the vaginal vault. The uterus could not be outlined. The abdominal mass was found to lie in the right fornix. At this time, the white cells had fallen to 12,200 with 82 per cent polymorphonuclear leucocytes; the red cells numbered 4.8 million and the hemoglobin was 91 per cent. The sedimentation time was over eighty minutes. A second roentgenogram of the chest (Fig. 2) showed a slight decrease in the pleural effusion on the right side.

On March 28, 1941, the patient was taken to the operating room and under 1 per cent procaine anesthesia the abdomen was opened through a six-inch suprapubic midline incision. The peritoneal cavity contained about 400 c.c. of straw-colored fluid. The uterus was small, posterior and lying in front of it, and extending upwards to a point 6 cm. above the umbilicus was a large, globular, gray-white, firm tumor of the right

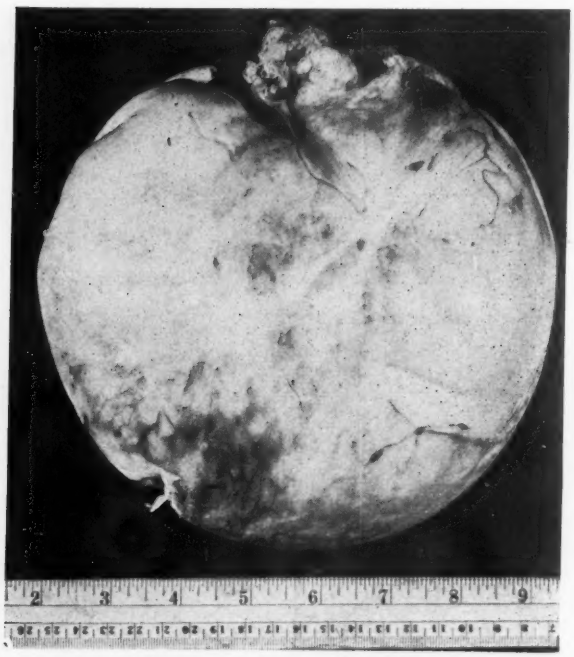

Fig. 4.—View of tumor. External surface was nodular, gray white in color, and the capsule was intact with many dilated veins coursing through it.

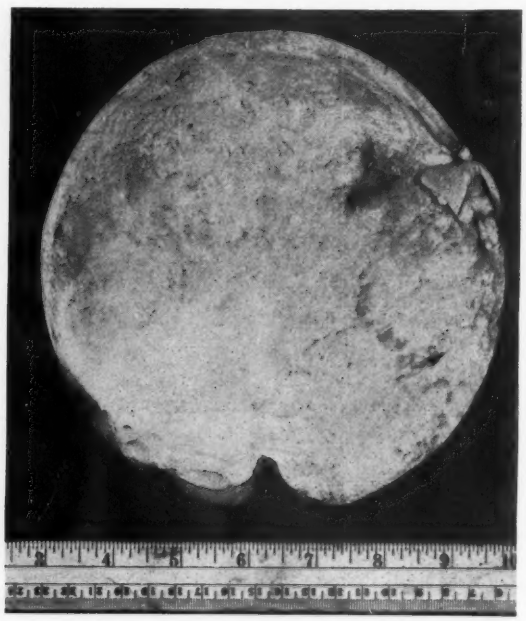

Fig. 5.—The cut surface of the tumor was gray white in color with a moderate-sized area of interstitial hemorrhage.

ovary. The fluid was aspirated, the neoplasm removed, and the abdomen closed with through-and-through black silk sutures.

The postoperative reaction was slight; the temperature rose to 100.4° F. and the pulse to 110 for the first two days. Gradually, these fell to normal and after forty-eight hours remained normal. On the sixth postoperative day, x-ray of the chest (Fig. 3) revealed that the fluid had entirely disappeared. On the tenth postoperative day, the patient was allowed out of bed, and on April 9, 1941, she was discharged in excellent condition. Since then, she has been seen on several occasions and has had no complaints. Neither the ascites nor the hydrothorax have recurred.

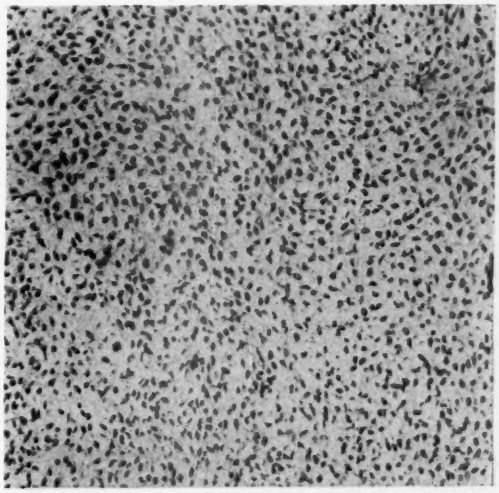

Fig. 6.—Microscopically, the neoplasm was comprised of broad sheets of spindle or oval fibroblasts.

Pathologic Report.—The specimen consisted of a large, oval mass measuring 18 by 16 by 10 cm. (Fig. 4). The surface was smooth, glistening, gray white in color with many small veins and venules coursing through its capsule. On section (Fig. 5) the tumor was made up of white whorls of fibrous tissue containing a large area of interstitial hemorrhage.

Microscopically, sections from various portions of the tumor revealed the same architecture and consisted of bundles of fibroblasts whose component cell was either oval or spindle in shape, contained moderate cytoplasm and an oval or spindle-shaped nucleus that took a deep stain (Fig. 6). In some areas, edema was prominent, producing a myxomatous-like appearance. Special stains failed to reveal the presence of fat.

Diagnosis: Fibroma of the right ovary with focal areas of hemorrhage and edema.

COMMENT

Despite suggestive signs and symptoms of cardiac disease and electrocardiographic evidence of myocardial fibrosis, this patient has been cured by the removal of the ovarian neoplasm. Postoperatively, the dyspnea, cyanosis, edema and fluid in both the pleural and abdominal cavities

entirely disappeared and have not recurred although she is actively engaged in housework and takes no medication.

The differential diagnosis must include pelvic malignancy with pleural and peritoneal metastases, tuberculosis, and cardiac failure. Here, only a tuberculous infection was easily excluded. Had operation been delayed, the result might have been fatal. Instead a cure was obtained. Consequently, it behooves the clinician to exercise extreme caution in offering a prognosis in those cases where a pelvic mass is associated with ascites and hydrothorax.

SUMMARY

1. A discussion of 18 previously reported cases of Meigs' syndrome is given.

2. Another case is reported in a woman of seventy-three years, the oldest of any of the reported cases.

3. The importance of establishing a diagnosis followed by surgical removal of the tumor is emphasized.

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AN EVALUATION OF A PARTICULAR MODE OF THERAPY OF TRICHOMONAS VAGINALIS

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THE purpose of this communication is first to correlate the hydrogen ion concentration of the vagina with the presence or absence of *Trichomonas vaginalis,* and, second, to evaluate the results of a particular mode of therapy.

Hesseltine's[1] communication brings the subject in many of its aspects to date. The pathology has been presented by Kessel and Gafford.[2] They biopsied the vaginal mucosa, including the petechial spots, and showed that the necrotic areas, only, harbor the flagellate. These workers have also shown the absence of the lactobacillus in trichomonas. Trussell and Plass[3] have infected women with pure cultures of trichomonas vaginalis. The work of Feo and collaborators[3] demonstrated that the *Trichomonas (hominis) intestinalis* is not a source of the infection.

They also have shown that the infection can be transplanted from fresh smears taken from the vagina, whereas pure cultures of *Trichomonas vaginalis* rarely infect.

From the data herein presented one must assume that acidity plays a definite part in this disease. The pH of the vagina was determined by means of the Beckman glass electrode which was inserted through a speculum, thus making direct contact with the vaginal wall. This method gave very accurate readings. For practical purposes the results using nitrazine indicator paper correlated well with the Beckman potentiometer readings. Therefore, in 50 per cent of the cases the nitrazine indicator method was used.

During this study, 145 pH determinations were made and the presence or absence of the flagellate noted. These are tabulated in Table I which shows that the trichomonas could be demonstrated in 13 out of 93 cases (20 per cent) at a pH of 5.5 or below, whereas above a pH of 6 their presence was demonstrated in 37 out of 52 cases (60 per cent). As shown, the flagellates are occasionally found at a pH below 5.5 and *can* be absent above a pH of 6 even though previously present in a patient with a pH of 6 before treatment. Trussell and Plass[4] observed that the trichomonas was better cultured above a pH of 5.5.

TABLE I

pH	POSITIVE	NEGATIVE
8	0	0
7.5	5	1
7	7	7
6.5	8	2
6	17	5
5.5	4	16
5	4	16
4.5	5	44
4	0	4

The treatment consisted of a douche containing one teaspoonful of lactic acid per quart of water. This gave a solution with a pH around 3.2. Following the douche, a compressed tablet containing 3.5 Gm. of B-lactose and enough citric acid and sodium bicarbonate to produce about 300 c.c. of CO_2 was inserted into the vagina. The gas produced served to spread the lactose throughout the vagina. It was necessary for the patient to wear a perineal pad, since the gradual solution of the lactose caused considerable drainage. It is believed that the lactose is utilized by bacteria to form more lactic acid, hence continuously keeping the vagina at a low pH. In twelve hours another douche was taken followed by the insertion of another tablet. This procedure was followed for twelve days; the patient was instructed to take no douche for two days before her visit. A few patients complained that the discharge from the tablet caused irritation and a burning sensation.

A total of 35 patients were followed four months to one year at bimonthly periods during the active stage, then monthly thereafter for three months. Fifteen of the patients were cured after two weeks' treatment, 4 after four weeks, 2 in six weeks, 3 in eight weeks, 1 in three months, 1 in four months, 3 in five months, and 1 in eleven months. There were four failures. Twelve patients had recurrences after apparent cure. In this series of cases there were 3 post-partum patients, 1 in early and 1 in late pregnancy, 2 having had recent abortions, 3 with chronic salpingitis, 3 harboring organisms following intercourse, 1 in the menopause, and 1 with chronic cervicitis. Most of the two-week cures were uncomplicated cases. In following these patients several reasons for failure to respond to treatment were noted and when corrected by the patient a cure usually followed. One of the reasons for unresponsiveness to treatment was a failure to insert the tablet well up into the vagina. Another was a lack of persistence in treatment, and a third was failure to carry out the treatment during a menstrual period. This last cause for failure was probably the most common, and is well accounted for by the fact that the vagina is relatively more alkaline during the time of catamenia.

A series of 27 cases using floraquin* tablets instead of the B-lactose tablets was similarly studied with comparable results.

SUMMARY AND CONCLUSIONS

The optimum pH for inhibition of *Trichomonas vaginalis* in the vagina is 5.5 and below. This hydrogen ion concentration can be maintained by means of dilute lactic acid douches and B-lactose. Eighty-eight per cent of the patients so treated were cured. Unknown factors account for the 12 per cent of failures.

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*The author wishes to thank the G. D. Searle and Company for their generous cooperation in supplying floraquin tablets for this study.

TREATMENT OF TRICHOMONAS VAGINALIS VAGINITIS WITH NEGATAN (NEGATOL)

WILLIAM FILLER, B.S., M.D., F.A.C.S., NATHAN DREZNER, B.S., M.D., AND FRANK H. ADAMO, B.S., M.D., NEW YORK, N. Y.

(From the Department of Obstetrics and Gynecology, New York University, College of Medicine and Bellevue Hospital, Gynecological Clinic)

FOR some years studies have been conducted in the gynecologic clinic at Bellevue Hospital in the treatment of *Trichomonas vaginalis* vaginitis, utilizing a number of different preparations and modes of therapy. No one therapeutic approach had ever proved so successful as to leave no room for another.

Since 1938, a new preparation, negatan (Negatol, Lilly) has been used in this clinic. The chemical and pharmacologic characteristics of negatan have been reported in an article[1] by the authors on the treatment of cervicitis with the same drug.

Eighty-seven cases of *Trichomonas vaginalis* vaginitis were treated in the following manner:

After a positive diagnosis was made by microscopic examination of the discharge, the vagina was cleansed with green soap, and dried. The vagina was then insufflated with negatan powder. The patient was instructed to douche with a tablespoonful of vinegar in two quarts of hot water the next night, following which she inserted a 20 per cent negatan suppository. This was repeated each night for one week, when she returned to the clinic for another insufflation and observation. Patients were often lax in returning regularly. However, no effort was made to record statistically such laxity. The criteria for cure consisted of three negative spreads after three successive menstrual periods without treatment during this time.

The results obtained in the treatment are given in Table II.

TABLE II

		AVERAGE NUMBER TREATMENTS	DURATION AVERAGE NUMBER DAYS
Cures	44 or 51%	8	103
Marked improvement (Symptomatic cure; at least one negative spread, but not observed long enough to be declared cures)	38 or 44%	7	66
Failures	5 or 5%	16	180
Total number of cases	87		

Although negatan failed to furnish uniformly good results in the treatment of *Trichomonas vaginalis* vaginitis, nevertheless, the results of this therapy are excellent in a condition which is often resistant to treatment.

The simplicity of the method, the relatively small average number of treatments required, and the absence of untoward effects were factors to recommend negatan. In addition, the time of treatment was short when one considers that an additional period of observation of approximately sixty days' duration was necessary in order to declare the patient cured.

In conclusion, the results of the treatment of 87 cases of *Trichomonas vaginalis* vaginitis with the new drug are sufficiently gratifying to recommend its use in the care of this often refractory condition.

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A CLINICAL NOTE ON THE USE OF SULFANILYLGUANIDINE IN MYCOTIC VAGINITIS

J. L. Pinkston, M.D., and John C. Burch, M.D., Nashville, Tenn.

(From the Department of Obstetrics and Gynecology, Vanderbilt University School of Medicine)

THE report by Marshall, Bratton, White, and Litchfield* of a reduction in the bacterial flora of the gastrointestinal tract following the oral administration of sulfanilylguanidine suggested the possibility of a similar action on the vaginal flora. In order to observe the effect of this drug in diseases of the vagina a random group of cases comprising the various forms of vaginitis was selected. The vagina was first cleansed with green soap and water, dried, and then insufflated with 3 Gm. of sulfanilylguanidine.† It was soon seen that this drug had a definitely beneficial effect on that form of vaginitis associated with mycotic infections. Since that time we have treated all of our cases of mycotic vaginitis with this drug. In most cases the drug has been applied by the patient to the posterior fornix of the vagina in gelatin capsules. Usually the application of 1 Gm. each morning and night, for a period of two weeks, will suffice. To date 20 patients have been treated by this method. In all cases the diagnosis was confirmed by a vaginal culture. Three patients reported symptomatic relief, but the cultures remained positive after treatment. Eight patients reported complete symptomatic relief but were unavailable for cultures at the conclusion of treatment. Nine patients reported complete symptomatic relief, and the cultures became negative for mycotic organisms. No evidence of toxicity of the drug was observed.

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*Marshall, Bratton, White, and Litchfield: Bull. Johns Hopkins Hosp. 67: 163, 1940.

†Supplied to us through the courtesy of Dr. David Brice of Lederle Laboratories.

Special Article

OBSERVATIONS ON THE ART OF MEDICAL ILLUSTRATIONS*

FREDERICK H. FALLS, M.D., CHICAGO, ILL.

IF ONE reviews the fields of art and medicine critically, two things stand out clearly. First, that many of the great artists were especially interested in the various phenomena of obstetrics and gynecology and second, that many of the great medical men tried to express their ideas in drawings no matter how crude and for the particular purpose of teaching their fellow physicians.

The best of the early attempts at art reproduction of men and events are the low bas-reliefs of the Egyptians and Assyrians. Later the Greeks used the high bas-relief and sculpture in the round. The designs were made in stone because of its endurance and availability. The earliest efforts were necessarily crude.

After the fall of Greece and through the Dark Ages very little was contributed to art of any kind throughout the world.

With the beginning of the Renaissance, there was a revival of art and the dawn of modern medicine. Leonardo da Vinci was the father of all medical art. His indomitable spirit and indefatigable mind led him to dissections of all kinds which he recorded carefully with full notes, in pen and ink and other media. His sketches which have come down to us are masterpieces of art. It was he who said: "The farther science develops the nearer it approaches art; the higher art develops the nearer it approaches science."

The first great team of medical illustrators with which we are familiar were Vesalius, the great anatomist, and Jan van Calcar, who made his drawings. They were markedly influenced by da Vinci's work and made many very creditable anatomic sketches.

Michelangelo, Luca della Robbia, and many other Renaissance artists concerned themselves with the depiction of motherhood, because of the religious importance of the Madonna and Christ child.

John and William Hunter left many sketches and drawings as records of their observations. So on down to our time when medical illustration has become a specialized field of art.

The average specialist in obstetrics and gynecology has had little or no opportunity to make a study of or even come in close contact with high grade medical illustrations. Even in the majority of medical colleges of the country the development of an art department has received scant attention or none at all. Almost universally, however, a medical specialist finds himself sooner or later in need of the services of a medical illustrator in connection with the production of books, lectures,

*Presidental Address at the fifty-fourth Annual Meeting of the American Association of Obstetricians Gynecologists and Abdominal Surgeons, Hot Springs, Va., September 11 to 13, 1941.

and magazine articles for publication. Since competent artists are so rarely found among medical specialists, he is fortunate indeed who can secure the advice and services of a skilled artist to assist him in projecting his ideas in a clear, dignified and forceful manner. Even when a good artist can be secured, the problem is not completely solved, for it is essential that the medical man appreciate both the possibilities and limitations of various forms of medical art, and that the artist have sufficient clinical experience and knowledge of the subject in hand to comprehend what the doctor wants to have emphasized. This teamwork is an essential part of good medical illustration in the field of obstetrics and gynecology.

The subject which I wish to present to you today is one which has held considerable interest for me for a number of years. To avoid any misconception, I wish to say that personally I have absolutely no artistic training or ability and to add that neither is essential to an understanding of this subject if one spends sufficient time to become acquainted with the problems and possibilities.

I have had the good fortune to have been rather closely associated with Mr. Tom Jones, Director of the illustrations studio of the College of Medicine, University of Illinois, for the past fifteen years. It has been most interesting and instructive to see first hand the work done by him and by the group of young artists associated with him.

One of his former students, Miss Charlotte S. Holt, has worked with me continuously for the past five years in preparing illustrations for a textbook, lantern slides for graduate and undergraduate teaching, and in the making of lay and professional exhibits for the educational program in maternal welfare in Illinois. Her collaboration has assisted in no small measure in making the visual educational part of the program outstanding.

From these contacts certain concrete ideas have been gleaned which I feel are of considerable value to medical men in the preparation of scientific communications, and which I wish to share with you with your permission.

In general, it may be said that medical illustrations fall roughly into several groups: photographs, line drawings, halftones, wash drawings, water colors and various types of models and charts for exhibit purposes.

CHARTS

One of the simplest and also most abused forms of medical illustration is the chart. There is a great temptation to crowd too much information on a single chart. Frequently also, the fault lies with the arrangement of the information on the chart rather than the amount of subject matter displayed.

To be of maximum value charts must have letters of sufficient size and simple style which stand out clearly enough to be read by the average person without eyestrain. The lettering should be clear, simple, and contrast sharply with the color of the background. For emphasis, when making lantern slides and charts for exhibit purposes, it may be of advantage to have certain sentences or paragraphs begin with words in color. Another device is to underline with colored or black lines important words or sentences.

Most charts must be framed if used for exhibit and teaching purposes since, if this is not done, they deteriorate rapidly due to handling, falling, packing, and other necessary usage. To minimize this risk we have found that covering the chart with pliofilm or similar transparent material and placing in a simple wooden frame will answer the purpose very nicely. Such charts are relatively lighter, less expensive and more durable than when glass is used for covering purposes.

Graphs are a form of chart and are subject to the same general rules. Frequently they are too crowded for comfortable quick reading, and as a result the information which they contain is difficult to appreciate by the average lay or professional audience, especially when they are presented in the form of lantern slides. In the interest of clarity the lines

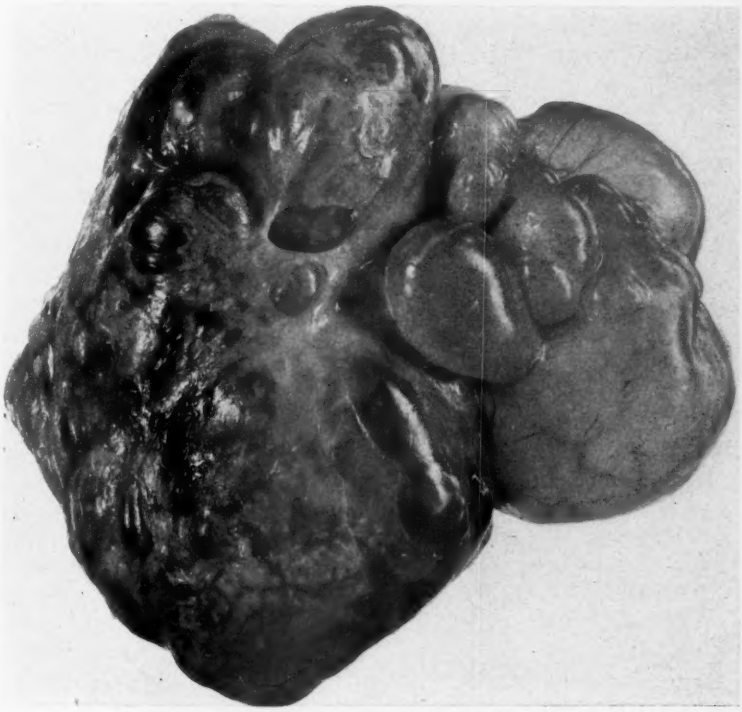


Fig. 1.—Example of black and white photography by Lawrence A. Toriello.

of the graph should not cross frequently if this can be avoided. Much writing or lettering in the body of the graph is undesirable. Both charts and graphs should have a clearly worded brief descriptive title, and if necessary an explanatory footnote may be added to clarify certain points.

PHOTOGRAPHS

Photographs are of great value for book or other illustrating purposes but, while most easily produced, they are the most undeveloped type of medical pictures. To be good illustrations and have scientific value they must be carefully taken of subjects correctly posed and illuminated. Snap shots of lesions and patients are for the most part useless. Good color photographs are even more difficult to make and are less satisfac-

tory because the colors are frequently exaggerated and not at all like the original in tonal value. Another objection is that with the present emulsions they tend to fade and change color in a few months or years, which seriously affects their permanent value. A great deal of research is being done to solve these problems and much improvement is to be expected in the immediate future.

Another weakness of the photograph is that the camera has no sense of selection and takes in everything within range on about the same dead level, whether of importance or not. In a drawing on the other hand, the artist can emphasize what the doctor wants brought out and subordinate the relatively unimportant details. Photographs have the advantage of speed in making and of usefulness as evidence in supporting some claim by the writer. They are also relatively inexpensive and have therefore the advantage that several photographs can be made of a given lesion and the best one selected, whereas, one drawing must, as a rule, suffice because of the expense involved in the production.

In illustrating a subject or lesion which is rarely encountered clinically and therefore difficult to present to the artist for first hand study, photographs of such lesions may be very valuable to the clinician in getting his ideas before the artist.

Photographs can also be enlarged or "blown up" for certain purposes and when printed on the proper type of paper can be tinted and made to appear almost like an original pastel or water color drawing. (Lantern slides can be made in black and white and then tinted with aniline dyes or colored photographs may be taken directly.)

Photographs of operative procedures taken at the time of operation have proved rather disappointing. It is difficult in many cases for the operator to pause at the precise point in the operation that he wishes recorded to allow the photographer sufficient time for correct focusing of his camera, the necessary light adjustment for proper illustration of the part to be photographed for his purpose, and the posing of instruments and personnel for the best results in the picture. Furthermore, unless the photographer is especially trained in operating room technique, there is considerable danger of serious contamination of the operative field.

The chief advantage of photographs is in depicting inanimate subjects, for example, an operating room setup; a complicated machine, such as the Drinker respirator, or to show the outside of a building, an operating room, or special instruments.

Photomicrographs are very valuable and can be displayed in black or white, or can be hand colored by an artist. Colored photomicrographs can also be made which are open to the same objections cited above for color photographs in general. Proper illumination of the slide and careful selection of the field to be photographed require time, patience and cooperation between the photographer and the surgeon.

The x-ray print is useful in illustrating certain phases of anatomy and pathology not otherwise easily demonstrated. It has the disadvantage however of being difficult to reproduce in half tone because of the frequent poor contrast in the original even when strongly illuminated. As a result retouching by hand by an artist is often necessary to secure the desired detail, which detracts somewhat from the validity of

the photograph. The x-ray illustrations in most textbooks are frequently very disappointing because these factors have not been taken into consideration by the writers.

Recently considerable advance has been made in photographing lesions of the cervix and vagina. For this purpose colored photographs have been used as well as black and white. The results have not been altogether satisfactory, however, because of the difficulty inherent to the problem which probably never can be completely eradicated, namely, that if the object to be emphasized, such as the anterior lip of the cervix, is in sharp focus, necessarily the rest of the field must be blurred, because it must be out of focus and therefore appears distorted.

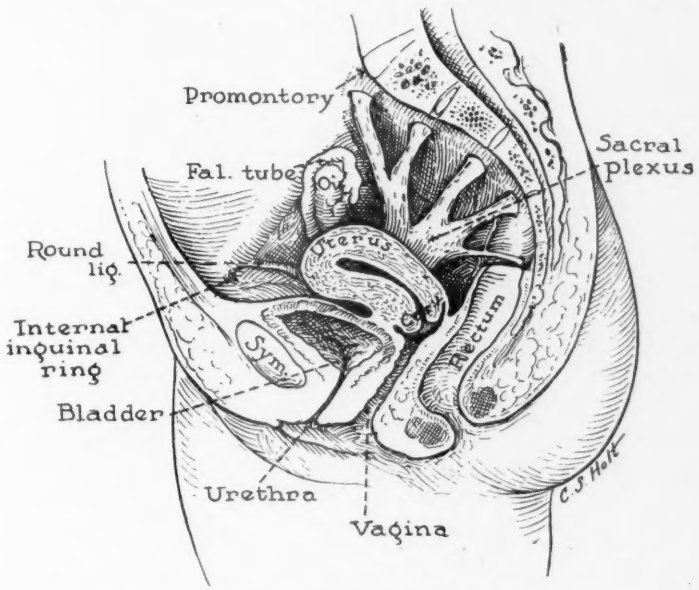


Fig. 2.—Example of a pen-and-ink drawing.

PEN-AND-INK DRAWINGS

The pen-and-ink drawing is very effective for many subjects and is often preferable to any other type of drawing. It has the advantage of sharpness of detail, simplicity and if well done carries the message with the least possible effort on the part of all concerned. To be effective such drawings should not be too complex and detailed, a mistake commonly made by some of the best artists a few years ago. When such great detail has to be shown, it is much better to use a wash drawing or a Ross board technique.

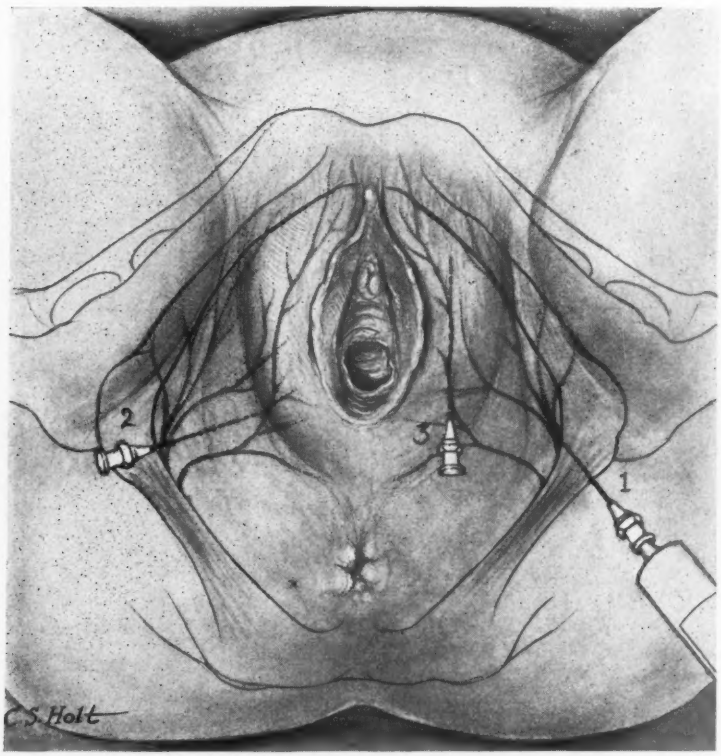
It is a good practice for the clinician to view the finished drawing through a reducing glass so that he may better visualize its appearance in the final publication before sending it to the publishers. Alterations can then conveniently be made if necessary.

While the simple black and white pen-and-ink drawing is very effective, it is frequently of considerable value to add color in the form of tinting to bring out some particular point to be emphasized. Under other

circumstances it may be advantageous to combine pen-and-ink and wash technique, and this can be done by an artist skilled in both methods with telling and pleasing effect.

It is also an important fact to be remembered that the reproduction of a pen-and-ink drawing for publication is only about one-half as expensive as that of a halftone. Another factor to be considered is that pen-and-ink reproductions can be printed on relatively low-grade and thin paper, whereas, halftone drawings and also colored plates must be

Local Anesthesia
Perineal block and infiltration



1, Blocking trunk of perineal nerve. *2*, Blocking branches in urogenital septum. *3*, Subcutaneous infiltration around vulval ring.

Fig. 3.—Combination of wash and pen-and-ink drawing by Charlotte S. Holt.

printed on a heavier book enamel stock which increases the size of a book appreciably when many illustrations are involved. The average printing establishment will turn out much better reproductions of pen-and-ink drawings than they will if halftones are submitted to them. However, first-class firms can handle either form of drawing equally well.

It may be pertinent to the discussion at this point to say that both the artist and author should demand proofs of all illustrations to go into an article or book, and should carefully proofread the same, noting defects and demanding good work. This of course can only be done when the originals supplied to the engraver are of good quality. It is surprising

how much better the finished article will appear if this simple precaution is taken. It is also true that most good publishers instead of resenting a request for illustration proofs appreciate the interest taken by the contributors.

The best all-around illustration, where utmost realism is desired, is the halftone. The clinician instinctively feels its usefulness and desirability, and usually requests it when other factors do not weigh too heavily in the balance. Its advantage is that it permits a wealth of detail and by skillful rendering of light and shade permits a realism which cannot be obtained in other forms of flat illustration. It can be done in black and white, and can be very beautifully combined with one or more colors. This technique can be used for publications or exhibit purposes, and lends itself well to photography, and can be reproduced beautifully

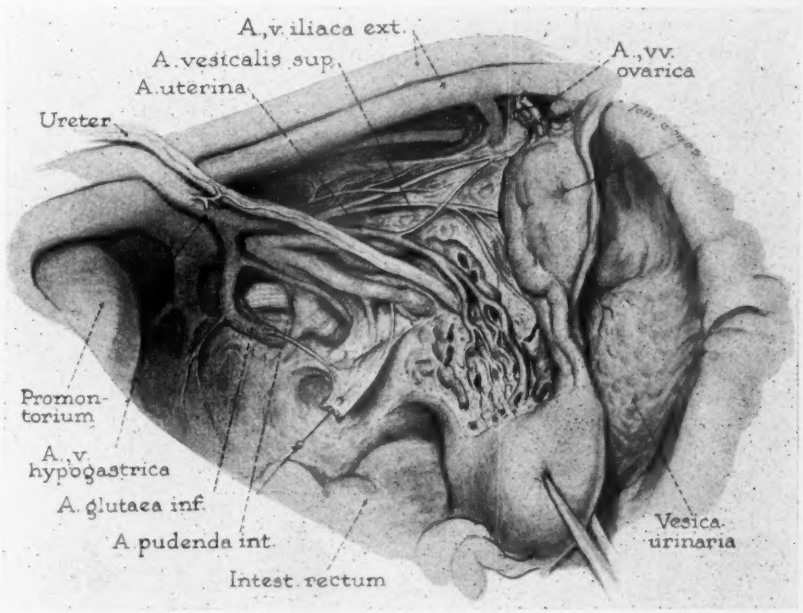


Fig. 4.—Example of wash technique by Tom S. Jones. (Curtis-Anson.)

in lantern slides. As mentioned above, it requires a somewhat heavier stock paper and is more expensive to reproduce properly than the pen and ink, and should not be submitted for reproduction to any except the best publishers. Within the last fifty years, Ross board technique has been used by some artists with very pleasing effect. This is a form of halftone illustration which depends upon obtaining shading, contrast and detail by use of a special Ross stipple paper and crayon dust. Max Brödel and his school have been the leading exponents of this method.

In the last few years a new approach has been developed in medical illustration by Dickinson and Belski in collaboration with Hoffman in New York, and Falls and Holt in Chicago. These workers have devoted themselves to making life-sized bas-relief models of obstetric subjects for exhibit and teaching purposes. Dickinson and Belski have depicted normal labor and the physiology of fertilization, while Falls and Holt have undertaken the reproduction of pathologic conditions, such as the

various types of ectopic pregnancy, premature detachment of the placenta, and contracted pelves, together with the complete reproduction of the operative steps in classical, low cervical and Porro cesarean sections, and the vaginal cesarean section. They have also a series of plaques showing the intrauterine development of the fetus at the various months of pregnancy.

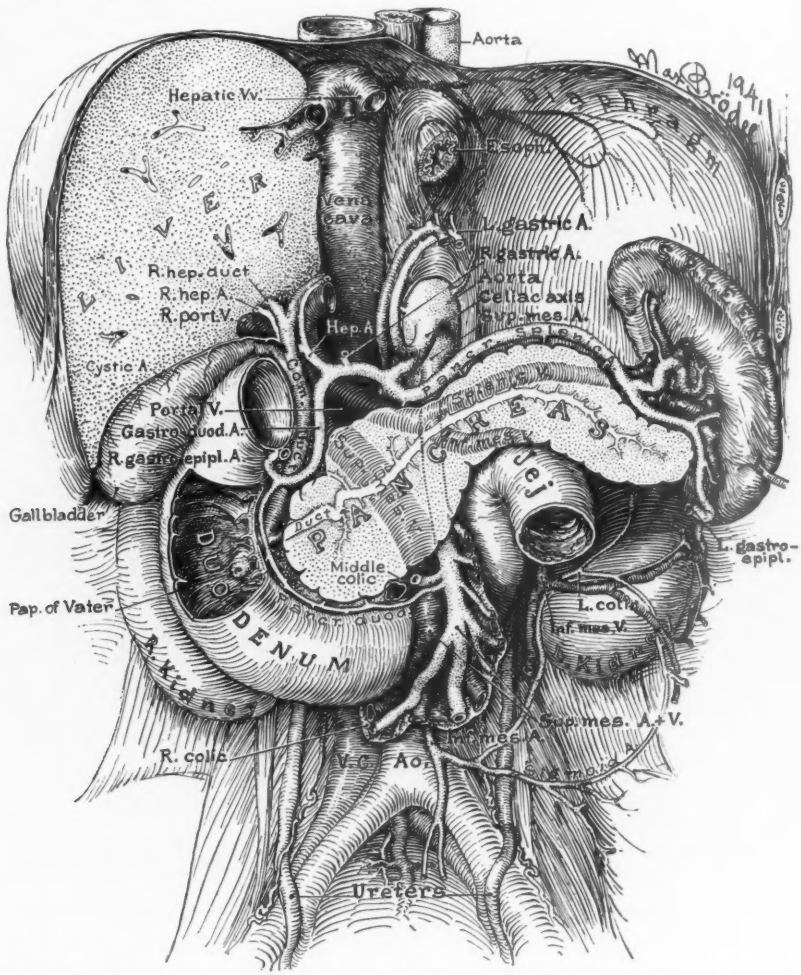


Fig. 5.—Example of pen-and-ink technique by Max Brödel. (By courtesy of Trimble, Parsons, and Sherman: *Surg., Gynec. & Obst.* 73: 712, 1941.)

This method of illustration requires considerable technical skill in sculpture on the part of the artist and the greatest degree of teamwork between the artist and clinician. Falls and Holt have developed a new technique for the development of these models which they feel will be an important contribution to medical education and medical art. The process consists of making first a sketch of the subject to be modeled. From this a bas-relief model is made in plastaline clay, life size if desired; and onto this is sprayed liquid latex (gum rubber) in several

coats which vulcanizes in air at room temperature. A plaster back is next made over the rubber which is removed after setting. The rubber is then stripped off the clay model positive and placed in the plaster back to act as a negative. It is then filled with hydrocale (artificial marble) which sets, and when removed from the rubber mold can be painted realistically in oils giving a most striking effect. The use of latex permits of casting undercuts which would be quite impossible with any other material heretofore used. It has also the advantage

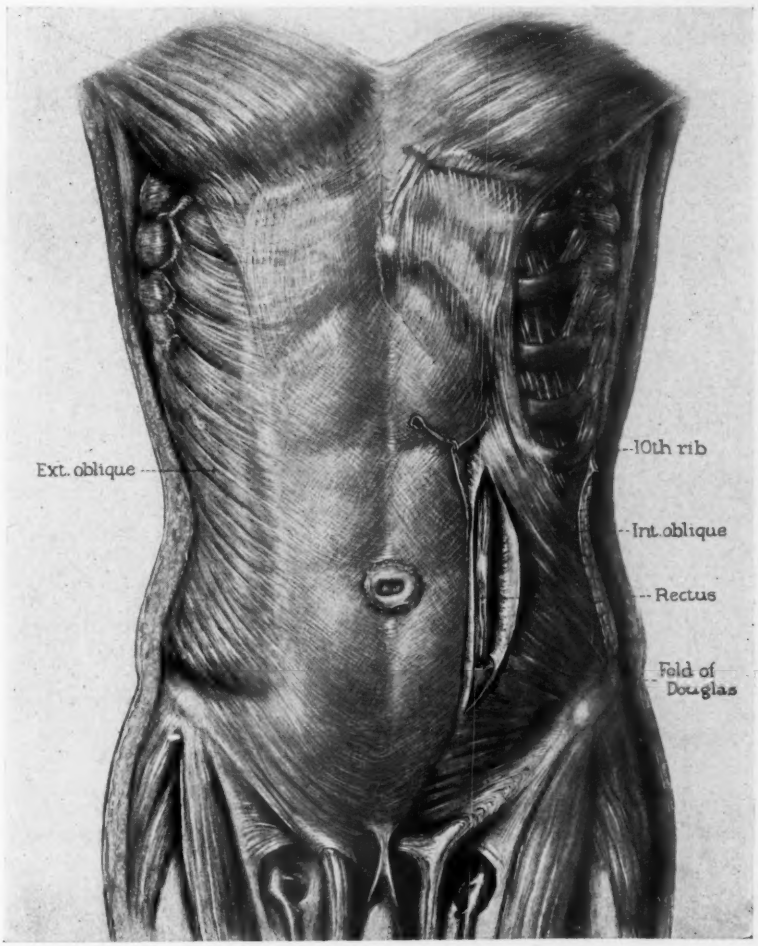


Fig. 6.—Ross board technique by Willard C. Shepard.

over most other materials used for making negatives, in that it can be used over and over instead of being destroyed by removal from the positive.

There is to my mind no doubt but that these models are the most valuable of all medical illustrative material for exhibit purposes because of the third dimension which produces a realism unattainable by other technique. When one adds life size and color painting, it leaves little to be desired.

The great drawback is the original cost of the materials for making the models, and for the time of the artist and clinician spent in making and remaking the sketches, clay models, and positives. However, the final product in artificial marble, which will outlast any other media, is worth the effort, especially since duplication by the method here indicated is comparatively inexpensive.

I have tried to outline in this address some of the factors which must be considered if satisfactory medical illustrations are to be produced. It is perfectly obvious to anyone who gives the matter more than casual consideration, that visual education is occupying more and more of the

Fig. 7.—Example of bas-relief model by Falls and Holt.

attention of medical teachers as well as those in other branches of education. Books without illustrations are almost a thing of the past. In many instances a book is judged more at least on cursory examination by the illustrations it contains than by the text.

It behooves us, therefore, if we are to keep abreast of the times, to consider carefully the type of illustration that will best suit the needs of a given publication, and to lend dignity and clearness to our presentations of medical contributions whether it be a lecture or published material, by providing appropriate drawings, slides, charts, or models. The desirability of pen and ink in one instance or a little color in another, a wash drawing here, a photograph properly posed and

illuminated there will give not only our audiences but also ourselves the highest degree of satisfaction.

Although much has been accomplished in recent years in this field, it is still a very young science. With the development of various forms of commercial art and the discovery and adaptation of new materials to old problems, the possibilities of finding new media to be used are enormous. It is for us a privilege to pioneer these new paths and to add our mite to the advancement of medical education.

The cost of medical illustration both for producing the illustration and in reproducing it in publications often may seem prohibitive, but if one considers the cost in time and effort on the part of the clinician to produce his part of the enterprise, and the permanent value of carefully done illustrative material, the outlay for the artistic side does not seem disproportionate.

Furthermore, it is remarkable how many different purposes a given drawing may fulfill. Thus we have made drawings of models to be used in an exhibit for medical men at the annual meeting of our State Society. These have been photographed and made into lantern slides which are used for undergraduate and postgraduate lectures to students, and to physicians who come to the University for short courses. Duplicate slides are sent out to County Medical Society meetings to illustrate postgraduate lectures. They are also used for nursing and even lay education when properly selected. Thus the use in many fields reduces the original cost very greatly.

Every educational institution offering medical courses should provide the members of its staff with facilities for good medical illustration if we are to advance in the field of medical education. I wish further to emphasize that it is not sufficient for trained artists and trained clinicians to attempt to produce good illustrative material at long distance. The artist must not only have the appreciation of his own field of work and technique, but he must also be given the clinical training necessary for him to appreciate the problem of presenting the ideas of the clinician to other physicians. It is, therefore, necessary for him to come in first-hand contact with the clinician and the patients, to see many operations on the subject under discussion, or to view first-hand fresh and preserved operative material so that he develops a knowledge of the fundamentals of the subject almost on a par with the physician. For this reason it is desirable and almost necessary for an artist in this field to have had considerable anatomy and some physiology and histology in his basic training.

For those of you who may be interested in art work, the time spent in assisting in the development of proper illustrations for your publications will soon be seen to be extremely valuable as a medium for clarifying in your own mind the essence of the subject material which you wish to present. It will necessitate an accuracy of detail which you would hardly have thought possible, and it will make you better medical men.

Society Transactions

NEW YORK OBSTETRICAL SOCIETY

MEETING OF JANUARY 13, 1942

The following paper was presented:

Clinical Experiments in Relation to the Excretion of the Estrogens. Dr. George van S. Smith (by invitation). (To be published in a later issue.)

MEETING OF FEBRUARY 10, 1942

The following papers were presented:

Tattooing With Mercuric Sulfide for Anogenital Pruritus. A Moving Picture Demonstration in Color. Dr. Robert Turrell (by invitation) and Dr. Samuel H. Geist.

Erythroblastosis Neonatorum. Dr. Carl T. Javert (by invitation). (For original article, see page 921.)

OBSTETRICAL SOCIETY OF PHILADELPHIA

MEETING OF JANUARY 8, 1942

The following papers were presented:

A Report of Twenty-Seven Years' Work in Control of the Midwives of Philadelphia County. Dr. William R. Nicholson.

Preparation of Obstetricians and Gynecologists for War Emergencies. Dr. Hubley R. Owen.

End Results in the Treatment of Carcinoma of the Cervix. Lewis C. Scheffey, M.D., William J. Thudium, M.D., and David M. Farell, M.D. (For original article, see page 941.)

Study of Maternal Deaths Due to Rheumatic Heart Disease. George L. Hoffman, Jr., M.D. (by invitation), and William Jeffers, M.D. (by invitation).

MEETING OF FEBRUARY 5, 1942

Devoted to a discussion of the Defense Program.

OBSTETRICAL SOCIETY OF BOSTON

MEETING OF NOVEMBER 18, 1941

The following paper was presented:

Studies in Renal Function in Normal Pregnancy and in Toxemia. Dr. Howard C. Taylor, Jr. (For original article, see page 567, April issue.)

MEETING OF JANUARY 20, 1942

The following study and case reports were presented:

Statistics on Cesarean Sections Throughout Massachusetts for 1940. Dr. Robert L. DeNormandie.

Delivery of a Double Headed Monster. Dr. Arthur F. G. Edgelow.

Bilateral Dermoid Cysts in the First Trimester of Pregnancy. Dr. Robert H. Goodwin.

Early Adenocanthoma of the Endometrium in a Twenty-Six-Year-Old Patient. Dr. Arthur T. Hertig and Dr. Paul A. Younge.

Department of Reviews and Abstracts

CONDUCTED BY HUGO EHRENFEST, M.D.

Selected Abstracts

Pregnancy and Disease

Minniti, Giuseppe: Collapse Therapy by Pneumothorax in Tuberculous Pregnant Women With Special Attention to Labor and Puerperium, Rassegna d'ostet. e ginec. **48**: 343, 1939.

The author reports upon 20 cases of pregnancy complicated by pulmonary tuberculosis. These patients were treated by means of collapse therapy during the course of their antenatal period and into the succeeding two months of the puerperium. All labors were normal. Low forceps applications were found necessary in but two of the deliveries. In no case was there evidence of exacerbation of the tuberculosis.

The author observed that artificial pneumothorax was compatible with the puerperal state. Except for unusual contraindications on the basis of more serious stages of the tuberculosis the disease can be treated by pneumothorax although the patient is pregnant.

The newborn infants of the mothers whose tuberculosis was treated throughout their pregnancies were found, as a rule, to be in even better states of nutrition than the infants borne by nontuberculous mothers of a similar age.

CLAIR E. FOLSOME.

Meixner, Fred M.: Pregnancy and Tuberculosis, Illinois M. J. **79**: 482, 1941.

The author gives six principles to be considered in the tuberculous pregnant woman: (1) No one has shown definitely that pregnancy is good for the health of a tuberculous woman in any stage or type of tuberculosis. (2) At least 75 per cent of the investigators believe that pregnancy aggravates tuberculosis, while no one has proved that abortion, properly performed, aggravates an early quiescent or arrested lesion, if proper tuberculosis therapy is followed afterwards. In certain far-advanced cases, abortion may act as a stimulus to the chest lesion, and noninterference is preferable if it is felt that abortion will mean death for both mother and fetus; whereas the continuance of pregnancy may mean the death of the mother, thus sacrificing everything for a live child. (3) Pregnancy places a severe strain on a tuberculous woman's resources and strength, and labor is fraught with immediate and remote perils. (4) After abortion or labor, chest therapy must be continued until the pulmonary condition is arrested. (5) Future pregnancies should not be allowed until after careful study has shown complete arrest. (6) Therapeutic abortion, when decided upon, should be done as early as possible under spinal or evipal anesthesia. X-ray technique for therapeutic abortion has a distinct value in pregnant tuberculous women.

When a better and more intelligent understanding of the problem on the part of the tuberculosis specialist and the obstetrician is reached, the pregnant tuberculous

woman may emerge from her pregnancy experience almost, if not quite, as safely as the nontuberculous woman, but until that time has arrived therapeutic abortion is indicated before the fourth month of pregnancy.

EUGENE S. AUER.

Baker, Robert H., and Ward, Arthur D.: Pulmonary Tuberculosis and Pregnancy, New England J. Med. **226**: 224, 1942.

The writers stress adequate and proper treatment of the tuberculosis during pregnancy which practically eliminates the necessity of therapeutic abortion. Under proper treatment, the associated pregnancy represents but little added risk. It is desirable to hospitalize these patients to secure care both of expert obstetricians and tuberculosis specialists.

Collapse therapy, preferably pneumothorax, should be instituted when possible and not discontinued during pregnancy. In active tuberculosis, this procedure is much more effective than abortion. After delivery vigorous therapy must be continued.

HUGO EHRENFEST.

Crabtee, E. G.: Pyelonephritic Injuries to the Kidney and Their Relation to Hypertension, J. Urol. **44**: 125, 1940.

A high percentage of pregnancy pyelonephritis cases show evidences of renal damage after five to eighteen years. Hypertension was present in 8 of 72 cases of pyelonephritis and in all of those that were complicated by toxemia. The relation of hypertension to the degree of renal damage was not always constant, but there was a closer relation of hypertension to the cases which showed marked renal insufficiency than to those which showed lesser degrees of damage to the kidneys. Hypertension is not the rule in cases of pyelonephritis pregnancy at from five to eighteen years after the infection.

J. P. GREENHILL.

Martius, H.: Etiologic Mechanism of Pyelitis of Pregnancy, Zentralbl. f. Gynäk. **65**: 812, 1941.

Martius calls attention to the anatomic relationship between the colon and kidneys. Both kidneys have an area which is apposed to the colon, the one on the right being larger. The photographs of the dissected specimens and sketches of the free lymphatic connections between colon and kidneys at these points vividly suggest the possibilities for the transit of *B. coli* to the renal tissues. It is perhaps significant in this respect that the coli pyelitis is more common on the right, when the hypotonic and plethoric colon lies against the hypotonic and overloaded right kidney over a relatively large surface. The author suggests that in view of these findings more attention should be paid to emptying the colon in the management of acute pyelitis of pregnancy.

R. J. WEISSMAN.

Jaameri, E.: Infections of the Urinary Tract Associated With Pregnancy and Particularly Those Following Complications of Labor, Acta. obst. & gynec. Scandinav. **20**: 306, 1940.

Under sterile precautions the author examined the urine of 600 pregnant or recently delivered women. He found organisms in the urine of 26.3 per cent. In this series 56 per cent were primiparas. Only 20 per cent of the women were aware of their infection and only 3 per cent of the healthy women complained of urinary

discomfort. Kidney disease seemed to be a predisposing factor in the etiology of infection of the urinary tract. Hyperemesis seemed to be a factor also. The author's study failed to ascribe to constipation any connection in the etiology of the urinary tract infections.

J. P. GREENHILL.

Heldfond, Alfred: The Treatment of Urinary Tract Infection of Pregnancy, West. J. Surg. **50**: 82, 1942.

The author reports the results obtained with various chemotherapeutic agents in the treatment of 145 cases of pyelonephritis in pregnancy. In his hands sulfathiazole proved most effective.

HUGO EHRENFEST.

Tonkel, E.: Some Remarks on the Metabolism of the Carbohydrates in Pregnancy, Monatschr. f. Geburtsh. u. Gynäk. **110**: 313, 1940.

The author emphasizes that the carbohydrate metabolism is altered during pregnancy. It is, therefore, impossible to compare the blood sugar curves of pregnant diabetics with those of normal nonpregnant women. During pregnancy, there is an increased opportunity for acidosis and coma to develop.

Diabetes during pregnancy is a dangerous complication. Insulin has reduced the maternal mortality but has had little influence on the fetal death rate. The pregnant diabetic women run much more risk of developing toxemia than nondiabetic women.

The treatment of diabetes during gestation is by means of insulin. Over-development of the child can be prevented by keeping the maternal blood sugar low. Furthermore, labor must be shortened, otherwise acidosis might develop due to fasting and vomiting which often takes place. Likewise, narcosis should be avoided whenever possible. One should not hesitate too long before performing a cesarean section in the interest of the child.

J. P. GREENHILL.

Nothman, H.: Diabetes Mellitus and Pregnancy, New England J. Med. **224**: 275, 1941.

Five diabetic women with a past history of several abortions and stillbirths were successfully delivered by prophylactic cesarean section. The high mortality rate of children of diabetic mothers may be decreased by this procedure. The influence that pregnancy will have on the diabetes of the mother cannot be predicted in any case, in spite of careful treatment. In the same patient, pregnancy at different times may take a very different course. A state of hypoglycemia in babies during the first days of life sometimes accompanied by periods of unconsciousness is described. The cause of this condition is the hypertrophy and overfunction of the pancreas.

Considering the extremely high mortality rate of the fetuses and children of diabetic women, prophylactic cesarean section offers a favorable outlook. Therefore, this procedure is recommended to save the life of the endangered fetus.

J. P. GREENHILL.

Grott, J. W.: Inflammation of the Pancreas During Pregnancy, Monatschr. f. Geburtsh. u. Gynäk. **112**: 77, 1941.

The author reports 12 cases of chronic inflammation of the pancreas discovered during pregnancy. From an analysis of these cases he insists that every woman in

whom glycosuria is discovered during pregnancy should have the pancreas examined, particularly during the puerperium. He describes a technique for manual examination of the pancreas.

J. P. GREENHILL.

Speiser, M. D.: Syphilis in the Pregnant Woman, New York State J. Med. 41: 240, 1941.

A special prenatal syphilis clinic was organized at Bellevue Hospital six years ago. In the last 16,437 deliveries, there were 790 patients diagnosed as having syphilis, an incidence of 4.8 per cent. In only 9 per cent was a history obtained of known syphilitic offspring who had either died as a result of their infection or were under treatment. Late abortions, premature deliveries, and term stillbirths occurred in 18.8 per cent of the cases, and in 24.7 per cent no significant data could be elicited in the history regarding a previous syphilitic infection.

The physical examination at the time of admission revealed early syphilitic lesions in 8.1 per cent of the patients and late lesions in 3.3 per cent. Therefore, 88.6 per cent of the patients with acquired syphilis were clinically latent. In the congenital group, manifestations were present in 65 per cent.

The value of serologic tests in establishing the diagnosis of syphilis is shown by the results of the tests in these cases. At Bellevue Hospital only the complement fixation test is employed.

While the effect of pregnancy upon syphilis offers a field for continued observation there is little doubt as to the disastrous effect of syphilis upon pregnancy. There were 95 untreated mothers who delivered 97 babies, and premature termination occurred in 51.5 per cent of the cases. In 81.5 per cent there were deaths due to syphilis or liveborn babies with syphilis, while only 13.4 per cent were free from the disease. Faulty presentation occurred in 12.4 per cent. In patients with early lesions who had received no treatment, 54 per cent had a morbid post-partum course. In the entire untreated group, the morbidity was 23.1 per cent.

A total of 566 cases were studied from the standpoint of the effect of syphilis upon pregnancy and the value of treatment. There were 517 babies delivered of 512 mothers who had acquired syphilis. Treatment given only during pregnancy salvaged 61.9 per cent of the babies, while treatment given both before and during pregnancy saved 92.1 per cent of the babies. A disastrous result in the latter group occurred in only 4.1 per cent, while in the former group it occurred in 25 per cent. Where treatment was started any time after the sixteenth week of gestation even in the absence of previous therapy, the incidence of prematurity was reduced to 14 per cent, disastrous results occurred in 29.5 per cent and 55.6 per cent were free of the disease.

The treatment of the syphilitic prenatal patient depends upon the absence of medical and obstetric contraindications, the stage of the syphilitic process, the length of gestation, and the tolerance for the drugs employed. A definite conclusion as to the status of the newborn child often cannot be reached before it is discharged from the hospital. Treatment should be withheld until a definite diagnosis is established.

J. P. GREENHILL.

Smith, Frank R., Jr., and Spence, John M., Jr.: Congenital Syphilis in Only One of Twins, South. M. J. 34: 147, 1941.

Of the 12 individual case reports dealing with this interesting condition which the authors encountered in a survey of the available medical literature, they considered only five completely acceptable because they possessed the essential criteria for this

diagnosis. These requirements are: (1) The congenital nature of the infection in the syphilitic twin must be clearly proved, and (2) the fact must be established beyond peradventure that the apparently non-syphilitic twin neither has had syphilis in the past nor is in the process of developing the disease.

Their own experience is based upon two cases personally observed. To the abstracts of these histories they have added two additional ones obtained from the records of the Johns Hopkins Hospital; the history of a fifth instance of this condition was supplied by a colleague. The fact that 4 of these 5 cases occurred among 44 twin gestations in 40 women with syphilis indicates that this anomalous phenomenon is not so rare as might be expected.

There are numerous hypotheses and theories, but no factual explanation for the occurrence of this condition. Of great significance is the fact that in the 5 cases reported all the twins were binovular. The authors conclude that, "the operation of sheer chance probably provides the best explanation."

ARNOLD GOLDBERGER.

Mankin, Z. W.: The Effect of Pregnancy and the Puerperal State on the Growth of Malignant Tumors, Arch. f. klin. Chir. **199**: 337, 1940.

A careful analysis of clinical developments in a considerable series of cases in which a pregnancy was complicated with a malignant growth somewhere in the body leads the author to the conclusion that the pregnancy by itself does not accelerate the growth of the malignant tumor, but that the deleterious effect follows labor, abortion, puerperium, and lactation. This holds true for cancers in the breast, uterus, intestinal tract, etc. Therefore nothing is gained by interruption of the intercurrent pregnancy, and as a matter of fact continuation of gestation to term often affords valuable time to deal with the malignancy before the puerperal or postabortal stage begins its inevitable aggravating effect.

HUGO EHRENFEST.

Brendler, F.: Conception and Spontaneous Childbirth With Previous Diagnosis of Carcinoma of the Cervix, Zentralbl. f. Gynäk. **64**: 1464, 1940.

The author discusses the confused state of knowledge of the effect of pregnancy upon the activity of uterine carcinoma. An interesting case is presented: A 42-year-old para ii was in good health until 1935 (aged 37), when she first experienced vaginal discharge and irregular bleeding. A suspected erosion was excised by her physician and on microscopic study was found to be a squamous cell carcinoma deeply infiltrating the tissues, but without outstanding cornification. In the stroma many secondary nests of cells were found. The patient refused further operation as she was now free of symptoms. Six months later she missed her first period and the following month a diagnosis of pregnancy was made. There were no symptoms of recurrence of the growth and nothing could be found on examination. Sudden bleeding and a rapid spontaneous delivery occurred during the eighth month of pregnancy. The woman was examined twice not long post partum and nothing abnormal was found.

Two years later irregular bleeding occurred, and after two months the patient appeared for examination which revealed a moderately sized exophytic tumor growing out of the cervix with a central crater admitting 1 finger. The growth was strictly confined to the portio. The parametrium appeared stiffened but not infiltrated. Histologically: squamous cell carcinoma with strong inflammatory reaction. Radium roentgen therapy was administered, and four months later on return for another treatment the vagina was found to be now a blind pouch. The left parametrium appeared stiffer than the right. There was no apparent recurrence and the patient

had gained 2½ kilos. At three-month intervals, until the writing of the report, no recurrence was found. The author feels that pregnancy is inimical to the activity of early carcinoma but that this may not be the case in pregnancy associated with well-established malignant growths.

R. J. WEISSMAN.

Putz, T.: The Healing of Fractures During Pregnancy and the Course of Labor After Fractures of the Pelvis, Monatschr. f. Geburtsh. u. Gynäk. 112: 17, 1941.

Three cases of fracture of the pelvis were observed by Putz at the Essen clinic. In the first case the patient was five months pregnant at the time of the fracture. She was able to walk four and one-half weeks after the accident occurred. Labor and the puerperium were uneventful. In the second case a severe fracture of the right thigh occurred during the eighth month of pregnancy. With the aid of Kirshner's wire extension, healing promptly followed. The third case of fracture of the pelvis was an old fracture in which the symphysis pubis had an opening, the breadth of a hand. In spite of this the patient had no difficulty in walking. Labor and the puerperium were uncomplicated.

The author points out that in spite of the favorable results in these three cases, fracture of the pelvis should not be considered lightly. In the literature there are cases where, following fracture of the pelvis, disturbances occurred, such as stillbirths and difficult forceps deliveries. Careful clinical x-ray examinations must determine whether the fractures result in hindrance to vaginal delivery or whether cesarean section is indicated.

J. P. GREENHILL.

Dyer, I.: Measles Complicating Pregnancy, South. M. J. 33: 601, 1940.

From an experience based upon the observation of 24 cases of measles complicating pregnancy, the author concludes that the coincidence of the two conditions is probably greater than the literature indicates; also, that the effect upon the pregnancy is not serious. These cases occurred in a rather widespread epidemic during the winter months in a rural community.

Provided that the mother has had the disease at least several months before delivery, the infant is protected from measles by an absolute immunity up to the fifth month, and by relative immunity up to the eighth month. Whereas there was no effect upon the pregnancy in 15 of these 24 cases, uterine contractions occurred in 11 cases. These were most frequently noted near the end of the period of incubation and on the first day of the eruption. In 9 patients termination of the pregnancy was attributed to the disease. Of these, 6 had reached or passed the thirty-eighth week of gestation, 2 were premature at thirty-three weeks and one aborted at eighteen weeks. Three infants had congenital measles; one of them contracted pneumonia at one month of age and died. A cesarean section was performed at the height of the exanthem and the infant was born with an extensive rash and Koplik's spots. Uneventful recovery occurred.

There was no maternal mortality, and in the one instance of morbidity a low-grade fever developed three weeks after the measles.

ARNOLD GOLDBERGER.

Mayr, Julius: The Question of Interruption of Pregnancy in Cases of Herpes Gestationis, München. med. Wchnschr. 87: 742, 1940.

Mayr discusses the symptomatology of herpes gestationis, and reports 6 cases. He states that the usual therapy, which consists of calcium, serum from normal pregnant

women, parathyroid hormone, sedatives and hypnotics, has no special value. The herpes may affect primiparas and multiparas, may appear at any time during pregnancy, although the prognosis seems to be worse the earlier in pregnancy the herpes appears. It has to be differentiated from impetigo herpetiformis, another pregnancy toxicosis which previously was considered serious enough to justify an interruption. But impetigo is due to a disturbance in the calcium metabolism and can now be completely cured with parathyroid hormone. In fact the success of the parathyroid hormone therapy aids in the differential diagnosis.

He concludes that the only therapy today for the severe cases of herpes gestationis is interruption of pregnancy and that the physician should not hesitate to undertake this procedure.

C. E. PROSHEK.

Kraines, S. H.: The Treatment of Psychiatric States Following Pregnancy, Illinois M. J. **80**: 200, 1941.

The author states that the incidence of puerperal psychoses among female admissions to mental institutions is from 5 to 10 per cent of all cases, and because general population psychoses occur in about the same proportion as puerperal psychoses, the inference can be drawn that pregnancy is the precipitating and not the causative factor in puerperal psychosis. In other words one may say that each person who develops a post-partum psychosis is psychotically predisposed.

The number of pregnancies which a patient has experienced does not seem to be significant. There are three common forms of the disease: (1) toxic; (2) schizophrenic; and (3) manic-depressive. The prepsychotic personality of these patients determines the form of their illness. Schizophrenic reactions are to be found most frequently in those persons whose pre-psychotic personality could be described as "introvert"; manic-depressive, in those whose tendency was to be "extrovert."

The treatment of psychiatric states following pregnancy is divided into three main categories. The first is the removal of toxic-infectious processes where they are discernible by the usual medical treatment. The clearing up of the infectious process will usually result in complete recovery of the toxic type of psychosis. The second form of treatment is convulsive shock treatment with either metrazol or electricity. The third form of therapy is psychotherapy which is directed toward the removal of the instability that exists in relation to the post-partum disturbance and the prevention of further neurotic disturbances. In those patients where the menstrual period is associated with emotional disturbance, testosterone propionate has been found useful.

EUGENE S. AUER.

Wick, Samuel: Puerperal Psychoses, Wisconsin M. J. **40**: 299, 1941.

Within 6 months seven patients were admitted to the Milwaukee County Hospital for Mental Diseases who had psychoses associated with the puerperium.

There were four with dementia precox, and three with manic-depressive psychosis of which one was depressed.

In 6 of the patients the first attack of mental illness was associated with pregnancy. It would seem likely that these women would not have had a mental illness if they had not been subjected to additional strain, both physical and psychic, incident to pregnancy. Unfortunately there are no definite signs to indicate which women should be advised against childbearing. Four of the patients in the series recovered and of the 3 who are unimproved, one has been ill four years, one for one year, and the third had a previous attack from which she recovered. The average duration of the psychosis in those who recovered was four months.

The treatment varies, depending on the symptoms which are present. In general these patients can be aided by early hospitalization where nutrition and fluids are maintained, elimination is increased, restlessness diminished, and exhaustion avoided. Insulin and metrazol therapy have been employed with the same results as in other cases of schizophrenia.

J. P. GREENHILL.

Schwaighofer, G.: Adrenal Insufficiency With Grippe in Pregnancy, Zentralbl. f. Gynäk. **64:** 1719, 1940.

Sudden and unexpected deaths occur in pregnant women contracting grippe. The author feels that the generalized swelling and hyperemia of the mucous membranes of the gravid woman allow easy permeation of bacteria and toxins. This, however, does not explain the sudden deaths in many cases. A 26-year-old gravida ii in the last month of pregnancy contracted influenza with bronchopneumonia. On the third day of her illness she suffered a peripheral vascular collapse with cold skin, empty veins, tachycardia, and tachypnea. There was no edema and no special findings were noted in heart or lungs. The fetal heart could not be heard. When the patient suddenly died, an immediate abdominal incision was made and a dead slightly macerated fetus was removed. At autopsy the lungs showed solely a hemorrhagic bronchitis; the heart was normal. Liver and kidneys showed cloudy swelling microscopically. Both adrenals, however, were enlarged and had hemorrhagic infarcts. In the right adrenal vein, a fresh dark red thrombus was found. The appearance was typical of adrenal apoplexy. Apparently as a result of parenchymal changes in infections, hyalin thrombosis takes place in venous capillaries, extending to the adrenal veins. Changes observed in the adrenal cortex are diminution and disappearance of lipoid droplets followed by vacuolation in the plasma with degeneration of cell nuclei. Congestion, hyperemia, edema of the gland and infarction follow. With the suspension of adrenal cortex function adynamia and other symptoms follow rapidly.

R. J. WEISSMAN.

Accivile, Dario: A Case of Acute Torsion of the Pregnant Uterus, Ginecologia **19:** 199, 1941.

The author describes a case of acute torsion of a pregnant uterus. The patient was 24 years of age and about three months pregnant. The torsion was complicated by a chronic appendicitis which had re-exacerbated to the subacute stage.

Laparotomy revealed the uterus to be rotated upon its isthmus a full 180 degrees from the left to the right. The left adnexal area was adherent to the ileocecoappendicular region. The left adnexal adhesions were freed, the pregnant uterus restored to its anatomic axis and the right adnexal tissue was removed with the offending appendix. The patient was confined by a normal delivery at term.

CLAIR E. FOLSOME.

Bowles, H. E.: Bilateral Ovarian Dermoid Cysts Complicating Pregnancy, West. J. Surg. **50:** 78, 1942.

To the so far reported 47 instances of the complication of pregnancy with bilateral ovarian dermoids Dr. Bowles adds five new observations, including one tubal pregnancy.

He believes that the optimum time for operation is the fourth month of gestation when placental hormones become active. Surgery should be done earlier only in the

presence of urgent symptoms suggestive of torsion, hemorrhage, etc. If the diagnosis is made only late in pregnancy, interference should be delayed until after viability, and then cesarean section done.

HUGO EHRENFEST.

Hoff, Franz: Torsion of the Ovary in Pregnancy, Ztschr. f. Geburtsh. u. Gynäk. **121**: 48, 1940.

A patient is described who, in about the thirty-fifth week of her fifth pregnancy, suddenly developed severe cramplike pain in the right lower abdomen. At operation an infarcted right ovary was found and removed. On the eighth day after operation she went into labor and was rapidly (thirty-three minutes) delivered of a normal living female child. The placenta failed to separate and was manually removed six hours after delivery. Mother and child had an uncomplicated subsequent course.

The literature dealing with torsion of tube, ovary, and both is discussed. The various theories of the etiology of the condition are critically examined. The author concludes that it arises as a result of a combination of various "predisposing factors" with other factors (Realisationsfaktoren) which produce the torsion when conditions are favorable. The most important predisposing factor is a congenitally elongated ovarian ligament. When this is present, mechanical factors tending to rotation and a hemodynamic factor (hyperemia, vascular obstruction) may act together to produce the torsion. It is the author's opinion that one of these alone is not sufficient.

The reported cases are listed in tabular form. The prognosis is good if the condition be recognized and surgical treatment quickly instituted.

J. L. MCKELVEY.

Kisimoto, Okai, and Torihudi: Intraabdominal Hemorrhage From Spontaneous Rupture of a Subserous Blood Vessel of the Uterus During Pregnancy, Japanese J. Obst. & Gynec. **23**: 238, 1940.

The authors report a case of a patient who was admitted to the hospital in the last month of pregnancy with a diagnosis of abruptio placentae. However, at operation it was found that the patient had a twin pregnancy with severe hemorrhage from a ruptured subserous blood vessel of the uterus. A supravaginal hysterectomy was performed. The patient recovered.

In the literature there are only 11 similar cases. In all of the cases the hemorrhage occurred spontaneously and the site of rupture was the posterior wall of the uterus. The most likely cause of the rupture of the blood vessel was friability of the wall of the vein involved. Overdistention of the uterine wall and other mechanical factors may play a role.

In not a single case of the literature was the correct preoperative diagnosis made. Prognosis is very bad; 8 of the 11 patients reported in the literature died. Furthermore, in most of the cases, the babies also perished. In the authors' case, the babies were dead before the operation was performed.

The treatment may consist of suture of the ruptured vessel followed by cesarean section, but often a Porro operation must be done.

J. P. GREENHILL.

Items

Continuation Courses in Gynecology and Obstetrics for Practicing Physicians

INSTITUTION	COURSE BEGINS	LENGTH AND CONTENT OF COURSE	NO. OF STUDENTS ACCEPTED	REGISTRATION FEE AND/OR TUITION	FOR DETAILED INFORMATION WRITE TO
		Gynecology			
Columbia University, including the New York Post-Graduate Medical School	Enter first Monday of any month when a vacancy occurs	15 sessions, MWF mornings or afternoons; Cystoscopy and Endoscopy	6	$75[8]	The Director, Columbia University School of Medicine, 309 East 20th Street, New York City
	Monthly	10 sessions, 3 mornings or afternoons a week; Diagnosis and Office Treatment	6	$40[8]	
	Monthly	15 sessions, MWF afternoons; Diagnosis and Office Treatment	6	$60[8]	
	Enter first Monday of any month when a vacancy occurs	24 sessions, TTS mornings; Gynecologic Endocrinology	4[2]	$100[8]	
	Arranged on application	4 or more hours weekly for 4 weeks or longer; Gynecologic Pathology		Arranged[8]	
	Arranged on application	12 sessions, TTS mornings, for 4 weeks; Surgical Anatomy as Applied to Operative Gynecology (cadaver)	2-3[4]	$200[8]	
Harvard Medical School, Courses for Graduates	June, July	Mornings for 1 month	4 per mo.[1]	$75	Dr. Frank R. Ober, Dean, Harvard Medical School, 25 Shattuck Street, Boston, Massachusetts
	Monthly	10 sessions, 2 mornings and evenings a week; Gonorrhea in Women	3	$20	

Obstetrics

Columbia University, including the New York Post-Graduate Medical School	First of any month from Jan. to Oct.	Full time for 3 mo.; Internship Training		$350	The Director, Columbia University School of Medicine, 309 East 20th Street, New York City
	First of any month	1 month; Observation Course		$100	
Duke Medical School and Hospital	Arranged on application through July 1 or later	5 days; Obstetrics and Pediatrics	4-6[20]	None[21]	Dr. G. M. Cooper, North Carolina State Board of Health, Raleigh, North Carolina
Harvard Medical School, Courses for Graduates	Monthly	1 month or more; Clinical Obstetrics	8[1]	$125	Dr. Frank R. Ober, Asst. Dean, Harvard Medical School, 25 Shattuck Street, Boston, Massachusetts
Indiana University, School of Medicine	Arranged on application	Arranged	10	$10	Dr. C. J. Clark, Chairman, Indiana University School of Medicine, Indianapolis, Indiana
	July 13	Full time, 2 weeks; Obstetrics and Gynecology	6[2]	$10[21, 22]	Dr. C. P. Huber, Director, Post-Graduate Course in Obstetrics, Indiana State Board of Health, 1098 West Michigan Street, Indianapolis, Indiana
Louisiana University Medical Center	June 1	2 weeks; intensive refresher course	Limited[23]	None[21]	Dr. V. E. Webb, Chief, Division of Maternal and Child Health, Louisiana Department of Health, New Orleans, La.
University of Nebraska, College of Medicine	Arranged on application	Full time, 2 weeks; Obstetrics, Gynecology, Pediatrics	2	$10[22]	Dr. C. W. M. Poynter, Dean, 42 Street and Dewey Avenue, Omaha, Nebraska

[1]Male physicians only.

[2]Physicians with adequate preliminary training and/or approved by the postgraduate department are eligible.

[4]Limited to specialists who have had preliminary training and experience.

[8]Upon application by physicians otherwise unable to meet the expense of postgraduate study, grants to defray part of the tuition are made from a scholarship fund.

[20]For state physicians. Some out-of-state physicians accepted.

[21]State boards of health furnish funds covering tuition fees, maintenance, or transportation for physicians of the state.

[22]All or part refunded on satisfactory completion of the course.

American Board of Obstetrics and Gynecology

The general oral and pathological examinations (Part II) for all candidates (Groups A and B) will be conducted at Atlantic City, N. J., by the entire Board, from Thursday, June 4, through Tuesday, June 9, 1942, prior to the opening of the annual meeting of the American Medical Association.

Group A, Part II, candidates will be scheduled for examination the first part of the examination period, and Group B, Part II, the latter half. Formal notice of the time and place of these examinations will be sent each candidate several weeks in advance of the examination dates.

As previously announced in the Board booklet, this fiscal year (1941-1942) of the Board marks the close of the two groups of classification of applicants for examination. Thereafter, the Board will have only one classification of candidates, and all will be required to take the Part I and Part II examinations.

The Board requests that all prospective candidates who plan to submit applications in the near future request and use the new application form which has this year been inaugurated by the Board. The Secretary will be glad to furnish these forms upon request, together with information regarding Board requirements. Address Dr. Paul Titus, Secretary, 1015 Highland Building, Pittsburgh (6), Pennsylvania.

Books Received

DISEASES OF METABOLISM. Detailed Methods of Diagnosis and Treatment. Edited by Garfield G. Duncan, M.D., Chief of Medical Service "B," Pennsylvania Hospital, Associate Professor of Medicine, Jefferson Medical College, Philadelphia, Pa. 158 illustrations and 7 plates in color, 985 pages. W. B. Saunders Company, Philadelphia, Pa., 1942.

INTERNAL MEDICINE IN OLD AGE. By Albert Mueller-Deham, M.D., Associate Visiting Physician, Welfare Hospital for Chronic Disease, etc., and S. Milton Rabson, M.D., Assistant Professor of Pathology, New York Post-Graduate Medical School, Columbia University, etc. 396 pages. The Williams & Wilkins Company, Baltimore, 1942.

THE BOND BETWEEN US. The Third Component. By Frederic Loomis, M.D. 267 pages. Alfred A. Knopf, New York, 1942.

THE HISTORY AND EVOLUTION OF SURGICAL INSTRUMENTS. By Dr. C. J. S. Thompson, with a foreword by Dr. Chauncey D. Leake. 115 illustrations, 113 pages. Schuman's, New York, 1942.

PEDIATRIC GYNECOLOGY. By Goodrich C. Schauffler, A.B., M.D., Assistant Clinical Professor of Obstetrics and Gynecology, University of Oregon Medical School, etc. 65 illustrations, 384 pages. The Year Book Publishers, Inc., Chicago, 1942.

UROLOGICAL DISEASES OF PREGNANCY. By E. Granville Crabtree, M.D., Urologist to the Boston Lying-in Hospital. With a chapter by George C. Prather, M.D., Assistant Urologist to the Boston Lying-in Hospital. 158 illustrations, many in color, 472 pages. Little, Brown and Company, Boston, 1942.

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